Molecular Advances in Retinitis Pigmentosa

IN THIS ISSUE of the journal, Farber, Heckenlively, Sparkes, and Bateman discuss the recent advances in the molecular biology of retinitis pigmentosa.[1] Retinitis pigmentosa and allied disorders are a group of hereditary diseases of the retina and choroid wherein retinal function is retained during the earlier years but eventually is lost as progressive cell dysfunction and cell death occur, resulting in blindness from loss of side vision, central visual acuity, or both.[2] This disorder is a leading cause of untreatable blindness in the young and early adult years. Classic retinitis pigmentosa can be inherited as either an autosomal recessive, autosomal dominant, or X-linked trait. Allied disorders include choroideremia, which is an X-linked recessive disorder, and gyrate atrophy, which is an autosomal recessive disease; both involve total vascular atrophy of the choroid and retina.[3] Retinitis pigmentosa can also be associated with systemic findings as part of a syndrome. Examples of syndromal association include the disorder as part of the Usher syndrome (congenital partial or profound deafness and retinitis pigmentosa), the Bardet-Biedl syndrome (congenital obesity, hexadactyly, hypogenitalism, the presence or absence of mental retardation, and retinitis pigmentosa), Alström's syndrome (diabetes mellitus, obesity, hypogenitalism, and retinitis pigmentosa),[4] and neuronal ceroid lipofuscinosis (also called Batten disease: retinitis pigmentosa, progressive gray matter deterioration, seizures, and early death).

Until recently, of the about 100 diseases grouped as retinitis pigmentosa and allied disorders, only 3 were understood at the biochemical or molecular level. Refsum disease was first described in 1946 under the name heredopathia atactica polyneuritiformis[5] and is associated with a defect in the α-oxidation of phytanic acid, causing the accumulation of this 20-carbon, fully saturated, branched-chain fatty acid in tissues, including the heart, nervous tissue, and the retina; in the retinal tissue, dysfunction and cell death finally cause blindness.[6] Other features include cerebellar ataxia, peripheral neuropathy, nerve deafness, ichthyosiform skin changes, and epiphyseal dysplasia. Cardiac conduction defects leading to arrhythmias are a major cause of early death in Refsum disease. Plasmapheresis may be required to lower plasma levels in acute cardiac toxicity, which can occur when phytanic acid is released from fat stores during fasting. Restricting phytanic acid from the diet can reduce serum phytanic acid levels to normal and has been associated, if acceptable levels can be maintained, with the preservation of vision.[7]

Abetalipoproteinemia is a systemic disease associated with acanthocytosis, progressive neurologic disease, and retinal degeneration.[8] Because of an inability to form chylomicrons, persons with this disorder usually present in infancy or early childhood with steatorrhea and intestinal malabsorption. A good screening test for abetalipoproteinemia is the serum cholesterol level, which, in patients with the disease, is extremely low, often less than 1.13 mmol per liter (50 mg per dl). Because of the absence of chylomicrons, fat-soluble vitamins A, E, and K cannot be transported from the intestinal lymphatics to the liver, and serum levels of these vitamins are extremely low. Treatment with large doses of vitamin A and E can slow or halt the progression of neurologic and retinal disease.

Gyrate atrophy of the choroid and retina is an autosomal recessive dystrophy[3] caused by a deficiency of the mitochondrial matrix enzyme, ornithine δ-aminotransferase (OAT), resulting in a failure of the conversion of ornithine to α-ketoglutarate and a failure of the production of proline.[9] Ornithine levels in serum reach 10 to 20 times normal. This enzyme is a pyridoxal phosphate-dependent enzyme system, and both vitamin B_6-responsive and -nonresponsive forms of gyrate atrophy have been reported. The molecular genetics of the inactivation of OAT have been recently studied.[9]

Rhodopsin is the photoreceptor visual pigment of the rods. Human retinas have about 100 million rods and 20 million cones. The gene for rhodopsin is known to lie on the long arm of chromosome 3.[10] Linkage studies of a large family in Ireland with autosomal dominant retinitis pigmentosa found strong, tight linkage to an anonymous DNA marker called C17,[11] which was known also to reside on chromosome 3. Because C17 and rhodopsin were also linked loosely to a third locus on chromosome 3 at about the identical linkage distance, Dryja and co-workers sequenced the gene directly for rhodopsin in autosomal dominant families with retinitis pigmentosa and found a C-to-A transversion in the second base pair of codon 23 of the rhodopsin gene.[12] This mutation, which, using an allele-specific oligonucleotide, was subsequently found to be present in about 12% of 150 families, changes the sequence to code for a proline residue instead of a histidine. The molecular defect was not found among normal persons or among unaffected members of the families. Indeed, when visual pigments and opsins of other species are screened, the proline at codon 23 is found to be well conserved in nature, again substantiating the defect as the cause of retinitis pigmentosa in these families. Soon thereafter, Dryja and associates described three other molecular defects of the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa.[13] At present, at least 30 separate molecular defects of the rhodopsin gene have been discovered, accounting for about 18% of all families with autosomal dominant retinitis pigmentosa.[14]

The tolerance of the rhodopsin gene to mutation is similar to that seen with the globin gene. Autosomal dominant retinitis pigmentosa does not appear to alter life expectancy or reproductive fitness. At present, how the specific molecular mutations alter rhodopsin physiology and produce cell dysfunction and eventual death is not well understood. The gene product appears, in general, to tolerate missense mutations over most of its amino acid sequence. Missense mutations in the region of the retinal binding site, however, such as Lys296Glu, appear to cause a more severe form of retinitis pigmentosa with no demonstrable rod function even at a young age.[15,16]

Cone dysfunction, cone cell death, and functional, if not virtual, blindness eventually develop in patients with this disease. It is difficult to understand how a defect in rod rhodopsin results in eventual dysfunction and cell death of cones as well. Theories have included the release of toxic products from degenerating rods or even sympathetic degeneration of cones. A transgenic mouse model has been created using the abnormal Pro23His mutation of rhodopsin,[17] and new transgenic mice models are being created for the other rhodopsin mutations. Future studies on these animals offer the hope of discovering the pathophysiology of how the molecular mutations cause retinal dysfunction and cell death. These studies promise new insights into the functions of cell regulation, maintenance, regeneration, and physiology.

Although no animal model exists in the wild that has a direct correlate in humans, the gene defects have recently been described at the molecular level for two mouse models for retinitis pigmentosa. Farber and colleagues at Jules Stein Eye Institute (Los Angeles, California) have for years studied the mouse model *rd*. This disorder begins with elevated cyclic nucleotide levels within the retina, followed later by progressive cell dysfunction and death.[18] The biochemical defect was uncovered by Farber's laboratory to be the enzyme phosphodiesterase, which is crucial for the regulation of the cyclic nucleotide cascade that is initiated by the process of visual excitation of the rod photoreceptor disc membranes.[19] Recently this same group found the β-subunit of phosphodiesterase to be the molecular defect in the *rd* mouse.[20] Although not confirmed as a primary defect, elevated levels of cyclic nucleotides were noted by the UCLA group in the retina of an eye from a person with autosomal dominant retinitis pigmentosa.[21] Travis and co-workers recently discovered that the gene responsible for the mouse model *rds* was the protein specific for photoreceptor outer segments called peripherin.[22] Peripherin is the gene product that helps photoreceptor outer segments form their membranes into discs. Retinas from *rds* mice show distorted, ballooned membranes instead of the normal discs.

Still, if those forms of retinitis pigmentosa that are known to result from mutation of the rhodopsin gene are excluded, this leaves 82% of cases of autosomal dominant, all forms of autosomal, and X-linked retinitis pigmentosa as undefined at the molecular level. At least two and possibly three genes for the disease reside on the short arm of the X chromosome, one at Xp11 and the other at Xp21.[23] Several candidate genes for retinitis pigmentosa are currently being investigated. Most, if not all, of these candidates are genes that are involved in either phototransduction, rhodopsin renewal, or rhodopsin regeneration. Specific candidate genes include the different subunits of G proteins (rod and cone transducins), the S antigen, the subunits of rod and cone cyclic guanosine monophosphate-phosphodiesterases, and several intracellular and extracellular retinoid binding proteins. Studies are now under way to screen families with autosomal recessive retinitis pigmentosa for defects of these candidate genes.

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Niacin—The Long and the Short of It

NIACIN IS ONE of the most effective agents for reducing levels of low-density lipoproteins and the triglyceride-rich lipoproteins of plasma. Experience with niacin for this indication now extends beyond 40 years. It is the only drug so far associated with increased survival in an intervention trial.[1] It has been shown to be synergistic with lovastatin and the bile acid-binding resins, leading to the development of combined regimens of unprecedented effectiveness.[2] The synergism of niacin with both of the other agents is such that therapeutic effectiveness can often be achieved at a fraction of the dose required if niacin is used alone. It appears to be the most effective agent available for lowering plasma levels of the Lp(a) lipoprotein. Furthermore, two recent quantitative angiographic trials using combined drug regimens that included niacin showed considerable regression of atherosclerotic lesions in the coronary arteries.[3,4] In evaluating the cost effectiveness of strategies of intervention in atherosclerosis, the extremely low cost of niacin makes it an attractive agent.

Niacin use, however, has a number of side effects with which physicians should be well acquainted if patients are to be successfully maintained on the drug therapy. Virtually all patients experience cutaneous flushing. This prostaglandin-mediated phenomenon can be mitigated substantially by slow, stepwise increases in dosage, beginning with 100 mg two or three times a day, by the administration of 150 to 300 mg of aspirin half an hour beforehand, and by taking the drug