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Editorial

New Era for Molecular Diagnosis of Retinitis Pigmentosa: From Research to Therapy

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Editorial

Retinitis pigmentosa (RP) is a clinical entity composed of a group of genetically heterogeneous retinal dystrophies. It has been known for a long time that RP consists of at least 3 different hereditary forms, i.e., autosomal dominant (AD), autosomal recessive (AR), and X-linked recessive (XL) traits; therefore, it has been thought that the putative causative genes for RP might also be heterogeneous. Due to the inability to completely analyze human genes up until the late 20th century, previous research has been unable to determine any of the disease mechanisms for RP, even though various combinations of biochemical, morphological, physiological and/or pharmacological studies have been undertaken. During the 1980's, however, evolutionally developed techniques and knowledge of molecular biology finally achieved a level that made it possible for researchers to use polymerase chain reaction (PCR) combined with nucleotide sequencing to relatively easily identify mutations in patients' genomic DNA. A landmark was finally reached in 1990 when Dryja reported for the first time a point mutation in the rhodopsin (*RHO*) gene in patients with one form of ADRP [1]. The discovery that mutations in the *RHO* gene caused RP opened up new research pathways that led many other researchers to try and find mutations in different retina-specific genes that might possibly be candidates responsible for causing RP. Currently, over 80 different causative genes have been reported to be responsible for RP [2,3] (also summarized in the RetNet: http//sph.uth.edu/retnet), which is far more than what was originally expected during the 1980's. Interestingly, although most of the causative genes for RP are specifically expressed in the photoreceptor or retinal pigment epithelial cells, some, such as the *PRPF31* gene, are ubiquitously expressed in numerous tissues other than the retina. The protein product of the *PRPF31* gene, i.e., PRPF31, is a component of the spliceosome [4] that is involved in the process of protein biosynthesis. Although previous molecular genetic studies have yet to reveal the entire causative genes for RP, we now know RP is caused by mutations in the genes that are responsible for encoding proteins specifically expressed in the photoreceptor cells or retinal pigment epithelium, or that are important in protein biosynthesis. These results have led to various hypotheses being proposed on the nature of the pathogenesis of the photoreceptor degeneration in RP. Between 1990~2000, discovery of causative genes and mutations attracted many researchers, as it was extremely exciting to be able to work on discovering a fundamental cause for RP, a disease for which the etiology was previously unknown.

After the initial enthusiasm in the search for mutations, the research focus gradually shifted toward trying to understand the mechanisms of photoreceptor cell death that occurred because of the gene mutations. Due to the genetic heterogeneity of RP, tailor-made therapeutic strategies that use gene therapy are being evaluated. Since mutation screening to identify a causative mutation among an entire genome can be extremely cumbersome, mutation-dependent treatment strategies are also being developed in which wild type genes are used to try to correct patients' defective genes. Conversely, it is also extremely important to try to understand the mutation-independent and common pathway of photoreceptor cell death in the genetically defective photoreceptors in RP. Despite the extreme genetic heterogeneity of RP, it was initially thought that a single pathway, i.e., caspase-dependent classic apoptosis, might be the final common mechanism of photoreceptor cell death [5]. Thus, if photoreceptor cells died due to a single metabolic pathway independent of gene mutations, e.g., caspase-dependent apoptosis, this would then mean that it should be quite simple to develop methods for photoreceptor protection in RP. However, experimental studies have not been able to demonstrate retardation of the photoreceptor degeneration when using a pan-inhibitor of the caspases [6]. Furthermore, recent studies of photoreceptor cell death have revealed that the mechanisms of photoreceptor cell degeneration are much more complex than what researchers had originally speculated [7,8]. The term programmed cell death (PCD) has recently been proposed as a way to identify the cell death mechanism, with the exception of accidental necrosis. Currently, PCD has been classified into apoptosis (caspase-dependent PCD), apoptosis-like PCD, and necrosis-like PCD [9]. Another study further suggested the classification of PCD should include apoptosis, necrosis, and autophagy [10], as it has been found that apoptosis and necrosis are closely linked by the receptor-interacting protein kinase (RIP) [11]. Once cells are unable to tolerate the intracellular stress caused by gene mutation, the PCD switch is turned on, and cell death begins to occur via one or more of the PCD pathways. Even when some of these pathways are blocked, cells continue to die due to alternative pathways. The pathway that is ultimately activated may also be mutation-dependent. For instance, two mutations, rhodopsin P23H and S334ter, show different PCD pathways during retinal degeneration [12]. These experimental results suggest that, even in the same gene or protein, different locations and kinds of mutations can trigger different PCD pathways.

Even though progress has been seen towards elucidating the mechanisms involved with photoreceptor cell degeneration, the question that needs to be answered is what do we need to do next in

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order to develop proper methods for photoreceptor protection against RP? One possible solution is to determine the proper combination of inhibitors that can be used against the various pathways of PCD. While this approach could be performed in a mutation-independent way, care needs to be taken depending on the mutation present, as these inhibitors could expose the patients to unnecessary agents. One other potential method is to use a combination of inhibitors against the mutation-specific PCD pathways. One alternative that has been suggested is to give a supplementation of 9-cis-retinoids to patients with RP caused by mutations in the RPE65 or LRAT gene [13,14]. A recent study has further shown that the 9-cis-β-carotene enriched alga, Dunaliella bardawil, may be useful in protecting against cone degeneration in RP caused by the RPE65 gene defect [15]. In addition, it was also experimentally shown that it is necessary to supply vitamin A to patients with RP caused by a rhodopsin gene defect [16]. Conversely, vitamin A supplementation may be harmful for patients with mutations in the *ABCA4* gene [17]. The overall findings from these studies do suggest that supplement-related photoreceptor protection is also mutation-dependent. Therefore, when a clinical trial involves heterogeneous groups of RP patients, it is generally difficult to prove specific beneficial effects of these substances for photoreceptor protection. Moreover, the genetic heterogeneity of RP can lead to discrepancies between clinical trials and animal experiments that utilize genetically homogeneous RP models. Thus, mutation-specific photoreceptor protection should be considered as a viable treatment option. Recent development of next-generation nucleotide sequencers and accumulation of mutation data for RP have helped make it relatively easy to identify patients' mutations, even in the clinical practices. In addition to the current development of specific gene therapies, we should also expect the introduction of new photoreceptor protection treatments that are more mutation-specific in the future.

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