BIOCHEMICAL FUNCTION OF THE LCA LINKED PROTEIN, ARYL HYDROCARBON RECEPTOR INTERACTING PROTEIN LIKE–1 (AIPL1)

Role of AIPL1 in retina

Matthew L. Schwartz, James B. Hurley, and Visvanathan Ramamurthy*

1. INTRODUCTION

Leber congenital amaurosis (LCA) is a clinically and genetically heterogeneous form of early-onset retinal dystrophy that is usually recessively inherited. LCA is the most rapid and severe form of congenital blindness, and it represents approximately 5% of all inherited retinopathies.1 Clinically, LCA is characterized by severely impaired vision and a weak or absent electroretinogram evident within the first year of life. To date, seven genes have been independently linked to LCA.2 The majority of mutations implicated in the causation of LCA are genetically consistent with recessively inherited loss-of-function pathogenesis mechanisms.2

The gene AIPL1 was originally identified by genetic analysis of patients with LCA.3 The gene was given the name AIPL1 (aryl hydrocarbon receptor-interacting protein like-1) because it encodes a protein (AIPL1) with sequence homology (49% identity, 69% similarity) to the protein AIP (aryl hydrocarbon receptor-interacting protein).3 Human AIPL1 contains 6 exons encoding a 384 amino acid protein that contains 3 tetratricopeptide repeat (TPR) domains and a C-terminal proline-rich region.3 The TPR domains are highly conserved amongst mammals, whereas the proline-rich region is thought to be present only in primates and shows considerable sequence variation amongst primates.4 AIPL1 is expressed exclusively in the retina and the pineal gland.3, 5, 6 During photoreceptor development in humans, AIPL1 is expressed in both rod and cone photoreceptors, but it’s expression is restricted to rods in the adult.7

AIPL1 mutations result in the most clinically severe forms of LCA, and it is estimated that AIPL1 mutations are responsible for approximately 7% of all LCA.8 LCA-linked muta-
tions include missense mutations, nonsense mutations, and short deletions.\textsuperscript{8} \textit{AIPL1} mutations linked to LCA are present in either the N-terminal immunophilin like domain (class I) or in the TPR domain (class II). Mutations in the C-terminal proline rich domain (class III) have been linked to dominant cone-rod dystrophy or juvenile retinitis pigmentosa and LCA.\textsuperscript{9}

2. ROLE OF AIPL1 IN RETINA- FINDINGS FROM AIPL1 DEFICIENT MICE

To elucidate the role of AIPL1 in the retina and to develop an animal model to study LCA caused by AIPL1 deficiency, we created an \textit{AIPL1} knock out mouse. \textit{AIPL1}\textsuperscript{-/-} mice demonstrate a phenotype consistent with LCA. Specifically, \textit{AIPL1}\textsuperscript{-/-} mice exhibit no measurable electroretinogram (ERG) response at any age and are completely blind at birth\textsuperscript{10} (Fig. 14.1). Ultra-structural details of the retina analyzed by electron microscopy show no obvious difference between wild type and knock out mice at post natal day 8 (P8) (Fig. 14.1).\textsuperscript{10} At P8, \textit{AIPL1} deficient mice show a normal complement of rod and cone photoreceptor cells with morphologically normal rod and cone outer segments. This suggests that \textit{AIPL1} does not play an essential role in the initial formation of rods and cone photoreceptor cells. At P11, the photoreceptor layer of the retina in the knock out mouse is morphologically indistinguishable from that of wild type by light microscopy, but ultra structural details observed by electron microscopy show disorganized and fragmented outer segments compared to wild type.\textsuperscript{10} This suggests that \textit{AIPL1} plays an essential role in either maintaining the outer segment and/or further photoreceptor cell differentiation after P9 in mice. The photoreceptor nuclear layer is reduced to half at P14 and at P18 the photoreceptor nuclear layer is only 1 cell thick in mice lacking \textit{AIPL1}.\textsuperscript{10} By four weeks after birth, the degeneration is complete (Fig. 14.1). Both rod and cone photoreceptor cells degenerate at a similarly rapid rate.\textsuperscript{10}

At the molecular level, differences between wild type and \textit{AIPL1}\textsuperscript{-/-} retinas appear earlier than the morphological differences. At P8, prior to the onset of retinal degeneration, \textit{AIPL1} deficient mice show reduced levels of cGMP phosphodiesterase (PDE) protein.\textsuperscript{10} The reduction in level of PDE is specific, as the levels of other photoreceptor-specific proteins such as Rhodopsin (Rho), Guanylyl cyclase (GC-E) are normal.\textsuperscript{10} All three subunits of PDE \textit{a}B\textit{g} are reduced by 90% despite normal levels of the mRNAs.\textsuperscript{10} Additionally, no cGMP-dependent PDE activity can be detected in the knockout retinas, implying that the PDE that is present in \textit{AIPL1}\textsuperscript{-/-} is dysfunctional. Consistent with the loss of PDE activity, cGMP levels are high starting at P8.\textsuperscript{10} Destabilization of rod cGMP PDE as a pathogenic mechanism has precedent in the mouse. The well-characterized \textit{rd} (retinal dystrophic) mouse results from a truncation mutation and/or a viral insertion in the rod PDE\textit{b} gene that causes a reduction in PDE\textit{b} mRNA and loss of rod cGMP PDE.\textsuperscript{11,12} In \textit{rd/rd} mice, there is a pattern of rapid photoreceptor cell degeneration similar to the degeneration that occurs in \textit{AIPL1}\textsuperscript{-/-} mice.\textsuperscript{12} However, there are significant differences between \textit{rd/rd} and \textit{AIPL1}\textsuperscript{-/-} mice.

In \textit{AIPL1}\textsuperscript{-/-} mice, both rods and cone photoreceptor cells degenerate at a similar rapid rate, whereas in \textit{rd/rd} mice, rods degenerate faster than cones.\textsuperscript{10,12} In \textit{AIPL1}\textsuperscript{-/-} mice there is no recordable ERG at any age, whereas in \textit{rd/rd} mice there are some cone responses at postnatal day 12.\textsuperscript{10,12} This is consistent with the fact that in humans, mutations in \textit{AIPL1} cause severe blindness that affects both rods and cones whereas deficiencies in PDE cause retinitis pigmentosa, primarily a rod disease.\textsuperscript{13}