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Bestrophin 1 and retinal disease

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ABSTRACT

Mutations in the gene *BEST1* are causally associated with as many as five clinically distinct retinal degenerative diseases, which are collectively referred to as the "bestrophinopathies". These five associated diseases are: Best vitelliform macular dystrophy, autosomal recessive bestrophinopathy, adult-onset vitelliform macular dystrophy, autosomal dominant vitreoretinochoroidopathy, and retinitis pigmentosa. The most common of these is Best vitelliform macular dystrophy. Bestrophin 1 (Best1), the protein encoded by the gene *BEST1*, has been the subject of a great deal of research since it was first identified nearly two decades ago. Today we know that Best1 functions as both a pentameric anion channel and a regulator of intracellular Ca^{2+} signaling. Best1 is an integral membrane protein which, within the eye, is uniquely expressed in the retinal pigment epithelium where it predominantly localizes to the basolateral plasma membrane. Within the brain, Best1 expression has been documented in both glial cells and astrocytes where it functions in both tonic GABA release and glutamate transport. The crystal structure of Best1 has revealed critical information about how Best1 functions as an ion channel and how Ca^{2+} regulates that function. Studies using animal models have led to critical insights into the physiological roles of Best1 and advances in stem cell technology have allowed for the development of patient-derived, "disease in a dish" models. In this article we review our knowledge of Best1 and discuss prospects for near-term clinical trials to test therapies for the bestrophinopathies, a currently incurable and untreatable set of diseases.

Contents

Abbreviations: AVMD, Adult-onset vitelliform macular dystrophy; ADVIRC, autosomal dominant vitreoretinochoroidopathy; ARB, autosomal recessive bestrophinopathy; BVMD, Best vitelliform macular dystrophy; Best1, Bestrophin 1; cBest1, Canine bestrophin-1; EOG, electrooculogram; ERG, electroretinogram; fhRPE, fetal human retinal pigment epithelial; hBest1, human Bestrophin 1; iPSC-RPE, induced pluripotent stem cell derived retinal pigment epithelium; mBest1, mouse Bestrophin 1; RPE, retinal pigment epithelium; RP, retinitis pigmentosa; TM, transmembrane; WT, wild-type.

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1. Introduction

The bestrophins were first identified in the human genome as a result of the association of *BEST1* mutations with Best vitelliform macular dystrophy (BVMD) (Marquardt et al., 1998; Petrukhin et al., 1998). To date, mutations in *BEST1* have been found in association with at least five clinically distinct retinal degenerative diseases. Following the association of *BEST1* (then known as *VMD2*) with BVMD, Kramer et al. identified three human homologues of *BEST1* initially termed VMD2L1, VMD2L2, and VMD2L3 (Kramer et al., 2004). The HUGO nomenclature committee has since reassigned names of the genes as *BEST1* (VMD2), *BEST2* (VMD2L1), *BEST3* (VMD2L2), and *BEST4* (VMD2L3). None of these homologues are known to be associated with human disease, though functional deficiencies in sweating (Cui et al., 2012) and maintenance of intraocular pressure (Bakall et al., 2008; Zhang et al., 2009) in *BEST2* knock-out mice suggest the possibility that *BEST2* mutations may have as yet unrecognized effects on human health.

Bestrophins are an ancient family of proteins and they exhibit a remarkable level of evolutionary conservation. They are found throughout the animal kingdom and have been identified in virtually every organism studied (Hartzell et al., 2008; Milenkovic et al., 2008). These diverse bestrophin-containing organisms range in complexity from simple bacteria (Yang et al., 2014), to eye-regenerating planarian flatworms (Cross et al., 2015; Lapan and Reddien, 2012), and finally to complex mammals (Bakall et al., 2003; Marmorstein et al., 2000). Although each bestrophin possesses unique physiological functions, they are invariably ion channels (Hartzell et al., 2008; Xiao et al., 2010). Within the phylogenetic tree, bestrophin shows a diverse array of gene orthologs as well as gene paralogs (Hartzell et al., 2008). All mammals studied to date have at least four vestigial paralogues (Hartzell et al., 2008), though Bestrophin 4 is a pseudogene in mice (Kramer et al., 2004). Insects, such as the fruit fly *Drosophila* and the mosquito *Anopheles*, also have four paralogs (Hartzell et al., 2008; Petrukhin et al., 1998). In contrast, the nematode species *Caenorhabditis elegans* has 25 bestrophin paralogs and the primitive chordate *Ciona savignyi* has just one bestrophin gene (Hartzell et al., 2008; Petrukhin et al., 1998). Between bestrophin orthologs and paralogs, the first 350 amino acids show the most conservation (Hartzell et al., 2008).

All four human bestrophin paralogs function as calcium-activated anion channels (Qu and Hartzell, 2008; Xiao et al., 2010). Other than being reportedly expressed in absorptive cells in human colon and small intestine (Ito et al., 2013), very little is known about the Bestrophin 4 protein. Bestrophin 3 shows a very broad tissue distribution and emerging evidence suggests that this anion channels plays important cell protective roles (Svenningsen, 2015) against endoplasmic reticulum stress (Lee et al., 2012), oxidative stress (Jiang et al., 2013), and inflammation (Song et al., 2014). Bestrophin 2 has been shown to mediate bicarbonate transport in colonic goblet cells (Yu et al., 2010) and compelling data indicates that Bestrophin 2 also mediates bicarbonate transport in sweat glands (Cui et al., 2012) as well as nonpigmented epithelium (Bakall et al., 2008; Zhang et al., 2009). Knockout mice lacking Bestrophin 2 suffer from a complete inability to sweat (Cui et al., 2012). *Best2* knockout mice also exhibit a significantly reduced intraocular pressure (Zhang et al., 2009, 2010).

Best1 is predominantly expressed in the retinal pigment epithelium (RPE) (Marmorstein et al., 2000). Within the RPE, Best1 is an integral membrane protein localized to the basolateral plasma membrane (Marmorstein et al., 2000). The human protein is comprised of 585 amino acids and, evolutionarily, the first ~350 amino acids of Best1 are highly conserved between species. Best1 has intracellular N- and C-termini, the latter of which is a large cytosolic domain comprised of approximately 280 amino

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