HotSpots

Mutations in CIB2 calcium and integrin-binding protein disrupt auditory hair cell calcium homeostasis in Usher syndrome type 1J and non-syndromic deafness DFNB48

References


Alterations of the CIB2 calcium- and integrin-binding protein cause Usher syndrome type 1J and non-syndromic deafness DFNB48

CIB2, also known as kinase interacting protein, belongs to a family of calcium and integrin-binding proteins and plays an important role in intracellular calcium signaling and cellular calcium homeostasis. Riazzudin et al. provide novel mechanistic insights into the causative association of homozygous mutations in CIB2 with the development of non-syndromic hearing impairment (DFNB48) and Usher syndrome J1 (USH1J). Using gene linkage and mutational analysis, the authors identified several allelic mutations in CIB2 (c.272T>C, p.Phe91Ser; c.297C>G, p.Cys99Trp; c.192G>C, p.Glu64Asp or c.368T>C, p.Ile123Thr) which cosegregate with deafness or deaf-blindness predominantly in Pakistani families. The carriers were found to possess normal hearing. Molecular modeling predicted that, depending on the location of the mutations, they alter the secondary structure of CIB2 and thereby weaken the CIB2–integrin interactions or increase CIB2 affinity for calcium binding (Fig. 1). These findings suggest that aberrant calcium homeostasis in stereocilia due to disruptive mutations in CIB2 may underlie deafness in the DFNB48-affected individuals. Importantly, the authors also found that CIB2 interacts with myosin VIIA (USH1B) and whirlin (USH2D), mutations in which are causatively associated with sensorineural deafness in USH1J.

The fact that intracellular calcium levels in stereocilia critically affect mechanoelectrical transduction, adaptation, frequency tuning and outer hair cell electromotility, a diverse array of mechanisms have evolved to keep calcium concentration in optimal range. Riazuddin et al. elegantly demonstrate the effects of functionally disruptive mutations in CIB2 on ATP-induced calcium release and how they can lead to sensorineural hearing loss and/or blindness. The fact that the authors also identified CIB2 to be part of the Usher interactome, which consists of a diverse array of proteins in hair cells of organ of Corti and photoreceptors (1, 2), genetic testing would enable pinpointing specific cases and aid in the differential diagnosis of congenital hearing and/or vision loss. Non-syndromic deafness accounts for approximately 70% of cases, majority (77%) of which show an autosomal recessive pattern of inheritance. Identifying the underlying genetic and molecular defect on individual basis has been difficult owing to two major reasons: (i) The inherent heterogeneity of the mutations, i.e. to date, more than 110 genetic loci and over 70 genes have been identified to cause congenital hearing loss, (ii) the next generation sequencing technologies, whereby analysis of several genes in a single test can be achieved, are not widely available. Nevertheless, these findings open up avenues for the development and implementation of molecular
therapies which could be used to correct disrupted
calcium homeostasis underlying inner ear dysfunction
and/or retinal degeneration in specific cases.

A Jan
Centre for Molecular Medicine and Therapeutic, University of British
Columbia, Vancouver, BC V5Z 4H4, Canada.,
e-mail: ajan@cmmt.ubc.ca