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Review

Molecular basis of human Usher syndrome: Deciphering the meshes of the Usher protein network provides insights into the pathomechanisms of the Usher disease

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Abstract

Usher syndrome (USH) is the most frequent cause of combined deaf-blindness in man. It is clinically and genetically heterogeneous and at least 12 chromosomal loci are assigned to three clinical USH types, namely *USH1A-G, USH2A-C, USH3A* (Davenport, S.L.H., Omenn, G.S., 1977. The heterogeneity of Usher syndrome. Vth Int. Conf. Birth Defects, Montreal; Petit, C., 2001. Usher syndrome: from genetics to pathogenesis. Annu. Rev. Genomics Hum. Genet. 2, 271–297). Mutations in USH type 1 genes cause the most severe form of USH. In USH1 patients, congenital deafness is combined with a pre-pubertal onset of retinitis pigmentosa (RP) and severe vestibular dysfunctions. Those with USH2 have moderate to severe congenital hearing loss, non-vestibular dysfunction and a later onset of RP. USH3 is characterized by variable RP and vestibular dysfunction combined with progressive hearing loss. The gene products of eight identified USH genes belong to different protein classes and families. There are five known USH1 molecules: the molecular motor myosin VIIa (USH1B); the two cell–cell adhesion cadherin proteins, cadherin 23 (USH1D) and protocadherin 15, (USH1F) and the scaffold proteins, harmonin (USH1C) and SANS (USH1G). In addition, two USH2 genes and one *USH3A* gene have been identified. The two USH2 genes code for the transmembrane protein USH2A, also termed USH2A (''usherin'') and the G-protein-coupled 7-transmembrane receptor VLGR1b (USH2C), respectively, whereas the USH3A gene encodes clarin-1, a member of the clarin family which exhibits 4-transmembrane domains. Molecular analysis of USH1 protein function revealed that all five USH1 proteins are integrated into a protein network via binding to PDZ domains in the USH1C protein harmonin. Furthermore, this scaffold function of harmonin is supported by the USH1G protein SANS. Recently, we have shown that the USH2 proteins USH2A and VLGR1b as well as the candidate for USH2B, the sodium bicarbonate co-transporter NBC3, are also integrated into this USH protein network. In the inner ear, these interactions are essential for the differentiation of hair cell stereocilia but may also participate in the mechano-electrical signal transduction and the synaptic function of maturated hair cells. In the retina, the co-expression of all USH1 and USH2 proteins at the synapse of photoreceptor cells indicates that they are organized in an USH protein network there. The identification of the USH protein network indicates a common pathophysiological pathway in USH. Dysfunction or absence of any of the molecules in the mutual ''interactome'' related to the USH disease may lead to disruption of the network causing senso-neuronal degeneration in the inner ear and the retina, the clinical symptoms of USH.

Keywords: senso-neuronal disease; retinal degeneration; retinitis pigmentosa; deafness; supramolecular network; interactome

1. Introduction

Human communication and perception of the environment are mainly formulated on information imported through the ear and the eye. Chronic diseases affecting the inner ear and the retina cause severe impairments of our communication systems. There are about 40 known human syndromes which include the symptoms of blindness in combination with deafness. In more than half of the cases, the Usher syndrome is the origin of this defect (Gorlin, 1995; Vernon, 1969). The human Usher syndrome (USH) is defined by congenital, bilateral deafness and a later onset of the loss of the visual field, caused

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by *retinitis pigmentosa* (RP). In RP, retinal degeneration is based on photoreceptor cell death which occurs from the periphery to the macula of the retina. Night blindness is the first symptom of RP, followed by narrowing of the visual field (''tunnel vision'') and later to complete blindness (van Soest et al., 1999; Wang et al., 2005). These visual deficits are triggered by any one of over 130 mutated genes (Tschernutter et al., 2005). USH is the most common cause of combined deaf-blindness (Vernon, 1969) and the most frequent form of recessive RP (Keats and Corey, 1999).

One of the earliest descriptions of USH was given by Albrecht von Graefe, a pioneer of modern ophthalmology. He reported a case of a deaf and dumb male patient with retinal degeneration who had two equally affected brothers (von Graefe, 1858). Subsequently his student Richard Liebreich, screened the population of Berlin for syndromes including RP and reported similar observations (Liebreich, 1861). He emphasized the recessive nature of the disease by commenting on the combination of congenital deafness with RP in several siblings from either consanguineous marriages or families with several members affected in different generations. The disease was eventually named after Charles Usher, a Scottish ophthalmologist who described the hereditary nature of this disorder in 19 cases out of 69 RP patients (Usher, 1914).

Based on the heterogenic clinical course of the disease described by Bell (1922) and Hallgren (1959) and co-workers, USH was subdivided into three clinical types, namely USH1, USH2 and USH3 (Davenport and Omenn, 1977). USH type 1 is the most severe form of this disease. USH1 patients are deaf at birth and the onset of RP is pre-pubertal. Most, but not all USH1 patients exhibit severe dysfunction of the vestibular system which leads to a further subdivision of USH type 1 (Otterstedde et al., 2001). USH type 2 is characterized by a constant moderate to severe hearing impairment from birth on and RP can be diagnosed during puberty (Reisser et al., 2002). USH type 3 (USH3) is distinguished from USH1 and USH2 by the later initiation of deafness combined with variable RP and vestibular dysfunction. In USH3 patients, the hearing impairment is progressive starting post-lingual and RP is diagnosed in most cases between the 2nd and 4th decade of life (Pakarinen et al., 1995; Petit, 2001). The classification into three USH types is still being used, although the increasing scientific knowledge through the end of the last century has revealed an even larger genetic heterogeneity to USH. To date, 12 independent loci on different chromosomes have been identified whose inherited defects lead to the development of USH. The loci defect dictates the subdivision into further subtypes, USH1A-G, USH2A-C, and USH3A as summarized in Table 1. Currently, an affected gene has been determined for eight different USH loci (Ahmed et al., 2003; Petit, 2001; Weil et al., 2003; Weston et al., 2004). However, in at least four of these genes, some mutations cause USH while others result in non-syndromic hearing loss. These USH genes are *MYO7A* for USH1B and DFNB2/DFNA11 (Liu et al., 1997b,c) and *CDH23* for USH1D and DFNB12 (Astuto et al., 2002; Bork et al., 2001), *PCDH15* for USH1F and DFNB23 (Ahmed et al., 2003) and *USH1C* for USH1C and DFNB18 (Ahmed et al., 2002; Ouyang et al., 2002). Some mutations in the *USH2A* gene cause isolated RP (Rivolta et al., 2000).

Epidemiological studies of USH show a prevalence of 3–6 patients per 100,000 inhabitants of the developed world (Boughman and Fishman, 1983; Forsius et al., 1971; Grondahl, 1987; Hope et al., 1997; Rosenberg et al., 1997; Spandau and Rohrschneider, 2002). Since false diagnosis of RP occurs frequently in infants, the prevalence is more likely to be 1/10,000 (Hope et al., 1997). The numbers of patients affected by the three distinct USH types is unequal. Studies in Europe show a proportion of 25–44% of USH1 patients and 56–75% of USH2 patients (Grondahl, 1987; Hope et al., 1997; Rosenberg et al., 1997; Spandau and Rohrschneider, 2002). Regional founder effects contribute to the described wide bandwidth of subtype prevalence. For example, USH3 in total accounts for a very low percentage ($\sim$ 2%), but in contrast contributes in

Table 1
Usher syndrome types: genes, proteins, functions, mouse models

Type	Gene locus	Gene	Protein	Cellular function	Mouse model
1A	14q32	*HEMAP ?*	EMAP	MAP (cytoskeleton)	–
1B	11q13.5	*MYO7A*	Myosin VIIa	Molecular motor	Shaker-1 (sh1)
1C	11q15.1	*USH1C*	Harmonin	Scaffold protein	*Deaf circler (dfcr)*
1D	10q21-q22	*CDH23*	Cadherin 23	Cell–cell adhesion	*Waltzer (v)*
1E	21q21	–	–	–	–
1F	10q11.2-q21	*PCDH15*	Pcdh15	Cell–cell adhesion	*Ames waltzer (av)*
1G	17q24-25	*SANS*	SANS	Scaffold protein	*Jackson circler (js)*
2A	1q41	*USH2A*	USH2A (usherin)	Matrix, cell adhesion	Knock outs
2B	3p23-24.2	*SLC4A7 ?*	NBC3	Ion co-transporter	k.o.: *Slc4a7 -/-*
2C	5q14.3-21.3	*VLGR1b*	VLGR1b	GPCR, cell adhesion	*Mass1 (frings), k.o.*
3A	3q21-25	*USH3A*	Clarin-1	Cell adhesion	k.o., in prep.
3B	20q	–	–	–	–

Description see text. MAP, microtubule associated protein. References: USH1A (Eudy et al., 1998; Kaplan et al., 1992), USH1B (Gibson et al., 1995; Kimberling et al., 1992; Weil et al., 1995), USH1C (Bitner-Glindzicz et al., 2000; Johnson et al., 2003; Smith et al., 1992; Verpy et al., 2000), USH1D (Bolz et al., 2001; Bork et al., 2001; Di Palma et al., 2001a, 2001b;Wayne et al., 1996; Wilson et al., 2001) USH1E (Chaib et al., 1997), USH1F (Ahmed et al., 2001; Alagramam et al., 2001a), USH1G (Kikkawa et al., 2003; Mustapha et al., 2002; Weil et al., 2003), USH2A (Eudy et al., 1998; Huang et al., 2002; Weston et al., 2000; Cosgrove et al., 2004; Liu et al., 2005); USH2B candidate (Bok et al., 2003; Hmani et al., 1999), USH2C (Johnson et al., 2005; Weston et al., 2004; Yagi et al., 2005), USH3A (Adato et al., 2002; Joensuu et al., 2001).