C. R. Biologies 337 (2014) 167–177

Contents lists available at ScienceDirect

Comptes Rendus Biologies

www.sciencedirect.com

Spotlight on vision

The retinal phenotype of Usher syndrome: Pathophysiological insights from animal models

Atteinte rétinienne dans le syndrome de Usher : contribution des modèles animaux à la physiopathologie

Aziz El-Amraoui [a,b,c,*], Christine Petit [a,b,c,d,*]

[a] *Institut Pasteur, unité de génétique et physiologie de l'audition, 25, rue du Docteur-Roux, 75015 Paris, France*
[b] *Inserm UMRS1120, 75015 Paris, France*
[c] *UPMC, 75015 Paris, France*
[d] *Collège de France, 75005 Paris, France*

ARTICLE INFO

Article history:
Received 3 December 2013
Accepted after revision 3 December 2013
Available online 20 March 2014

Keywords:
Usher syndrome
Deafness
Retinitis pigmentosa
Hair cell
Hair bundle
Photoreceptor cell
Calyceal processes

ABSTRACT

The Usher syndrome (USH) is the most prevalent cause of inherited deaf-blindness. Three clinical subtypes, USH1–3, have been defined, and ten USH genes identified. The hearing impairment due to USH gene defects has been shown to result from improper organisation of the hair bundle, the sound receptive structure of sensory hair cells. In contrast, the cellular basis of the visual defect is less well understood as this phenotype is absent in almost all the USH mouse models that faithfully mimic the human hearing impairment. Structural and molecular interspecies discrepancies regarding photoreceptor calyceal processes and the association with the distribution of USH1 proteins have recently been unravelled, and have led to the conclusion that a defect in the USH1 protein complex-mediated connection between the photoreceptor outer segment and the surrounding calyceal processes (in both rods and cones), and the inner segment (in rods only), probably causes the USH1 retinal dystrophy in humans.

Mots clés :
Syndrome de Usher
Surdité
Rétinite pigmentaire
Cellule ciliée auditive
Touffe ciliaire
Photorécepteurs
Processus caliciels

RÉSUMÉ

Le syndrome de Usher (USH) constitue la première cause de cécité-surdité héréditaire. Trois sous-types cliniques, USH1–3, ont été définis, et dix gènes USH ont été identifiés. La déficience auditive due aux défauts des gènes USH résulte d'une désorganisation de la touffe ciliaire des cellules sensorielles. À l'inverse, la base cellulaire du défaut visuel est beaucoup moins bien comprise, car il manque dans presque tous les modèles murins de USH, qui reproduisent pourtant fidèlement la déficience auditive. Les différences inter-espèces structurelles concernant les processus caliciels de la cellule photoréceptrice et leur association avec la localisation des protéines USH1 ont récemment été mises en évidence. Elles ont conduit à la conclusion qu'un défaut dans la connexion médiée par les protéines USH1 entre le segment externe du photorécepteur et, d'une part, les processus caliciels (à la fois dans les bâtonnets et les cônes) et, d'autre part, le segment interne (dans les bâtonnets seulement) est probablement à l'origine de la dystrophie rétinienne USH1 chez l'homme.

* Corresponding authors. Unité de génétique et physiologie de l'audition, Inserm UMRS1120, département de neuroscience, Institut Pasteur, 25, rue du Docteur-Roux, 75015 Paris, France.
E-mail addresses: aziz.el-amraoui@pasteur.fr (A. El-Amraoui), christine.petit@pasteur.fr (C. Petit).

1631-0691/$ – see front matter
http://dx.doi.org/10.1016/j.crvi.2013.12.004

1. Introduction

The Usher syndrome (USH), an autosomal recessive genetic disease, is responsible for more than a half of the human cases of inherited deaf-blindness. This syndrome was first described by Albrecht von Graefe in 1858, but was named after Charles Usher, a Scottish ophthalmologist, who was the first to report the hereditary nature of the disorder (Usher, 1914) (see references [1,2]). Previous epidemiological studies have estimated the prevalence of USH as 1/25,000 [3], but more recent studies have proposed prevalence ranges from 1/6000 [4] to 1/10,000 [5] as there can be frequent misdiagnosis of the retinitis pigmentosa. USH is clinically and genetically heterogeneous. Studies concerning the properties of USH proteins, their interacting partners, and the phenotypes of USH deaf mutant mice have elucidated the molecular and cellular mechanisms underlying the USH hearing impairment and the roles played by the USH proteins in the cochlea (see references [6–8]). In contrast, little is known about the pathogenesis of vision impairment, as there is a lack of significant visual defect in most USH mutant mice (see references [2,6,7,9,10]). In this review, we focus on recent results that shed light on the pathogenesis of the USH retinal phenotype. We also discuss future therapeutic approaches aimed to prevent or delay the onset of retinitis pigmentosa in USH patients.

2. Clinical features and molecular diagnosis of Usher syndrome

Three types of USH (USH1, USH2, and USH3) have been distinguished clinically. These are defined according to the severity of the sensorineural hearing impairment, the presence or absence of vestibular defects, and the precocity of retinitis pigmentosa onset (Table 1) (see references [7,8,11–13]). USH1 is the most severe form. USH1 patients have severe to profound congenital bilateral hearing loss, which, if uncorrected, impedes speech acquisition. Vestibular dysfunction is also present from birth; USH1 children acquire the ability to take a sitting position and to walk later than usual. The USH1 retinopathy is classified as a rod-cone dystrophy, in which rod anomalies appear first and rapidly worsen, followed by a slow progressing cone dysfunction, and photoreceptor cell degeneration [9,13–17]. Night blindness may be detected during childhood, and this can be followed by a narrowing of the visual field (“tunnel vision”), which rapidly progresses to more severe blindness [2,18]. Retinal degeneration over the course of the disorder can be followed by the progressive reduction in electroretinogram (ERG) wave amplitudes and by fundus examination. Abnormal ERG responses may be recorded in patients prior to the symptoms of retinitis pigmentosa arising, and can help early disease diagnosis; the earliest age at which ERG abnormalities have been reported in USH1 children is 18 months [14–17,19]. USH2 patients display moderate to severe congenital hearing impairment (mostly affecting high sound frequencies). Speech is usually not affected, and vestibular function is normal. Symptoms of rod-cone dystrophy manifest later in USH2 patients than in USH1 patients, as the retinitis pigmentosa is usually diagnosed in USH2 patients between the ages of 10 and 40 [20,21]. USH3 is the least common type of USH but has a high prevalence in Finns and Ashkenazi Jews, likely as a result of founder effects (see reference [13]). In USH3 patients, hearing impairment starts before the age of 30, and is progressive. The progression speed is variable but, in most cases, patients ultimately become profoundly deaf. USH3 patients have well-developed speech. The vestibular defect is variable, and the onset of retinitis pigmentosa is postpubertal, usually starting from the age of 20.

Visual dysfunction is clinically diagnosed at an average age of 17 and 24 in USH1 and USH2 patients, respectively [14–17,19]. Such a late diagnosis has detrimental consequences for USH individuals. To date, about 14 different USH loci have been mapped on different chromosomes (see http://hereditaryhearingloss.org/), and 10 of the corresponding genes have been identified (Fig. 1). These genes encode six USH1 proteins – myosin VIIa (USH1B) [22], harmonin (USH1C) [23,24], cadherin-23 (USH1D) [25,26], protocadherin-15 (USH1F) [27,28], SANS (USH1G) [29], and CIB2 (USH1J) [30], three USH2 proteins – usherin (USH2A) [31], VLGR1 (USH2C) [32], and whirlin (USH2D) [33], and one USH3 protein, clarin-1 (USH3A) [34] (see Fig. 1). In addition, *PDZD7* has been shown to act as a modifier of USH2 gene function [35]. Whether *PDZD7* is also an USH2 causative gene remains to be established.

Private mutations are common in USH patients [36]; thanks to improving sequencing techniques, sequencing of the exons of all known USH genes is the best method for an early and reliable molecular diagnosis of the disease ([36–38]; see references [8,12,39]). Improvements in molecular diagnosis are still needed for all causative gene anomalies (such as large deletions, and modifications to introns and promoters) to be detected. The USH molecular diagnosis is critical for genetic counselling, educational orientation, the use of prosthesis (especially cochlear implants in USH1 patients to improve their speech acquisition), and the initiation of any new therapy under development. For example, patients may have learnt to use sign language (inefficient once they undergo visual

Table 1
Clinical characteristics of Usher syndrome (USH) subtypes. Three types of USH (USH1, USH2, and USH3) have been distinguished clinically. Indications regarding the evolution of speech acquisition by affected kids, their acquisition of the sitting position, and walking abilities should help to discriminate among the three USH subtypes.

	Hearing impairment	Vestibular dysfunction	Retinitis pigmentosa
USH1	Profound and congenital	Severe	Prepubertal onset
USH2	Mild to severe and congenital	Absent	Postpubertal onset
USH3	Mild and progressive	Variable	Postpubertal onset or variable