Biochimica et Biophysica Acta 1828 (2013) 167–178

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

The role of connexins in ear and skin physiology — Functional insights from disease-associated mutations ☆

Ji Xu [a], Bruce J. Nicholson [b,*]

[a] *Department of Physiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA*
[b] *Department of Biochemistry, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA*

ARTICLE INFO

Article history:
Received 4 March 2012
Received in revised form 23 June 2012
Accepted 29 June 2012
Available online 13 July 2012

Keywords:
Connexin 26
Connexin 30
Deafness
Skin disease
K^+ recycling
Hemichannel

ABSTRACT

Defects in several different connexins have been associated with several different diseases. The most common of these is deafness, where a few mutations in connexin (Cx) 26 have been found to contribute to over 50% of the incidence of non-syndromic deafness in different human populations. Other mutations in Cx26 or Cx30 have also been associated with various skin phenotypes linked to deafness (palmoplanta keratoderma, Bart–Pumphrey syndrome, Vohwinkel syndrome, keratitis–ichthyosis–deafness syndrome, etc.). The large array of disease mutants offers unique opportunities to gain insights into the underlying function of gap junction proteins and their channels in the normal and pathogenic physiologies of the cochlea and epidermis. This review focuses on those mutants where the impact on channel function has been assessed, and correlated with the disease phenotype, or organ function in knock-out mouse models. These approaches have provided evidence supporting a role of gap junctions and hemichannels in K^+ removal and recycling in the ear, as well as possible roles for nutrient passage, in the cochlea. In contrast, increases in hemichannel opening leading to increased cell death, were associated with several keratitis–ichthyosis–deafness syndrome skin disease/hearing mutants. In addition to providing clues for therapeutic strategies, these findings allow us to better understand the specific functions of connexin channels that are important for normal tissue function. This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

© 2012 Elsevier B.V. All rights reserved.

Contents

1. Introduction 168
2. Connexin phenotypes affecting the ear and epidermis 168
    2.1. Cx26 mutations and non-syndromic hearing loss (NSHL) 168
    2.2. Cx26 mutations and syndromic deafness 169
    2.3. Other connexin mutations in deafness and skin disease — Cx30, 30.3 and 31 169
3. Function of connexins in the ear 170
    3.1. Connexin distribution in the ear 170
    3.2. Functional properties of the major cochlear connexins (Cx26 and 30) 170
    3.3. Insights from mouse genetic models 172
    3.4. Proposed models for gap junction function in the ear — insights from functional deficits of connexin deafness mutants 172
        3.4.1. K^+ recycling 173
        3.4.2. Metabolite transfer 175
        3.4.3. A role for hemichannels? 175
        3.4.4. Relative roles of Cx26, 30, 30.3 and 31 175
4. Function of connexins in the skin 175
5. Prospects for the future 176
Acknowledgement 176
References 176

☆ This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

* Corresponding author at: Department of Biochemistry, Mail Code 7760, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA. Tel.: +1 210 567 3772; fax: +1 210 567 6595.
E-mail address: nicholsonb@uthscsa.edu (B.J. Nicholson).

0005-2736/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2012.06.024

1. Introduction

As the sole mediators of the direct exchange of ions, signaling molecules (cAMP, IP_3, etc.), energy sources (ATP, GTP), reducing/oxidizing agents (glutathione) and nutrients (glucose, amino acids) between cells, it is not surprising that gap junctions have been implicated in the homeostatic and integrative functions of most tissues. However, unlike other membrane channels and transporters, where the nature of the signals involved is well established, it has been hard to define the specific underlying mechanisms of this integration of cell behavior, as the identification of the relevant gap junction permeants has proven challenging for these relatively non-specific channels. Nonetheless, extensive evidence from several in vitro and mouse studies has shown that different connexin isotypes cannot substitute for one another and create normal tissue functions, demonstrating that not all connexins are created equal. The picture becomes even more complex with the growing recognition that at least some connexin proteins can also form open hemichannels on the plasma membrane under certain physiological conditions (reduced extracellular Ca^{++}, depolarizing membrane potentials and membrane stretch — [1–3]). This would provide one of the few known routes for the exchange of larger molecules between the cytoplasm and extracellular space. In fact, they have been implicated in ATP release associated with Ca^{2+} wave propagation [4], nicotinamide-adenine dinucleotide (NAD^+) release to allow access to CD38 and conversion to cADP ribose [5], and PGE_2 release to regulate bone formation [6]. In addition, the cytoplasmic domains of several connexins, particularly Cx43, have been shown to interact with a number of important structural and signaling molecules (reviewed in Ref. [7]), suggesting additional pathways by which they may be able to influence cell behavior.

Given the broad spectrum of roles connexins can play in integration of cell behavior, it is not surprising that mutations associated with several members of the connexin family have been associated with a diverse array of diseases affecting many tissues (neuronal myelin, eye (lens) and ear (cochlea) structure and function, connective tissue, cardiac function, etc.; reviewed in Ref. [8]). These diseases not only challenge us to seek the means to alleviate their symptoms, but also provide a unique window into understanding the specific functions of connexin proteins in different tissues. Nature has provided us a host of mutations that affect different aspects of channel functions. When these are associated with specific patient phenotypes, and accompanying mechanistic studies in mice engineered to express the defective proteins, we take major steps towards defining their mechanism of action in specific tissues. This becomes increasingly important in the case of gap junctions, as most of the powerful genetic model systems (e.g. *Drosophila melanogaster* and *Caenorhabditis elegans*), which have provided invaluable insights into function in other gene families, are of limited use in the study of the connexin gene family, as gap junctions in most invertebrates are composed of a topologically similar, but unrelated family called innexins. The relatives of innexins in vertebrates, a 3-gene family called the pannexins, appear not to form gap junctions, but either forms surface hemichannels or plays as yet undefined roles in intracellular compartments [9,10].

Perhaps the most widely studied example of connexin-associated disease has been the role of Cx26 (GJB2), and to a lesser extent the other β-connexins Cx30 (GJB6), 30.3 (GJB4) and 31(GJB3), in hearing loss. This is in large part due to the sheer frequency of these mutations, five of which can account for large fractions of all cases of prelingual, non-syndromic deafness in different human populations. In addition to these primarily recessive mutants associated with non-syndromic deafness, other mutations with dominant inheritance patterns have been associated with combined deafness and skin disease phenotypes, and yet others cause problems only in the skin. This constellation of mutations, affecting only 3–4 closely related proteins, provides a unique set of "controls" that help in dissecting out which functions of connexins are critical in the two tissues. There have been several excellent reviews on this topic over the last few years [11–13]. Thus, rather than providing an exhaustive listing of all cases of connexin-associated deafness and skin disease, we will focus on mutations in each of the above disease types where we have some information on the functional consequences, and attempt to summarize what this has taught us about the likely roles of gap junctions in maintaining normal cochlear and skin functions.

2. Connexin phenotypes affecting the ear and epidermis

2.1. Cx26 mutations and non-syndromic hearing loss (NSHL)

1 in every 1000 children could suffer from congenital hearing loss [14], which can be either syndromic or non-syndromic. Non-syndromic hearing loss (NSHL) is characterized by sensorineural hearing loss in the absence of other symptoms, while syndromic hearing loss affects other organ systems, primarily the skin in the case of connexins. The loci linked to non-syndromic hearing loss could be categorized into dominant (DFNA), recessive (DFNB), X-linked (NFDX), and Y-linked (NFDY).

Over 80 loci have been linked to nonsyndromic hearing loss, covering a large spectrum of molecules critical for the normal function of the ear [15]. However, mutations in GJB2 (encoding Cx26) account for half of all congenital and autosomal recessive non-syndromic hearing loss (DFNB1) in every tested population [16–24]. To date, there have been over 150 mutations found in the GJB2 gene. Among these mutations, deletion mutations which cause frameshift and/or truncation of the protein at an early stop codon are the most frequent. Several mutations are present with high prevalence, but with different frequencies in different populations. 35delG [17–22,24], 167delT [23,25], 235delC [16,26], R143W [27] and W24X [28,29] mutations are, respectively, prevalent in Caucasian, Jewish, east Asian, Ghanan, and Indian/Romani gypsy populations. These mutations have carrier frequencies between 1 and 4%, and contribute to between 30 and >80% of the cases of congenital sensorineural deafness in each of these populations. The high frequency of these mutations has been variously attributed to founder effects, or structural features of the genome (e.g. a string of repeated Gs in the case of 35delG) that increase the likelihood of mutation. However, another possibility that has been proposed is that these mutations could confer some selective advantage [13]. 35delG and R75W carriers have been reported to have a thicker epidermis [30,31], with the latter heterozygotes also showing higher sweat salinity. These phenotypes may confer a higher resistance to injury or microbial infection. This is also consistent with an observation that Cx26 wt, but not the R75W mutant, rendered HeLa cells more subject to invasion by the gastrointestinal pathogen, *Shigella flexneri* [32].

Although the most frequently occurring NSHL mutations produce severely truncated proteins due to frameshift or missense mutations, almost 80% of the described deafness mutations are actually single amino acid changes or deletions. As summarized in [12], these mutations have been found in all domains of Cx26. However, the significance of this is unclear without any information on the functional effects of these mutants. Fortunately, the last few years have seen increasing numbers of these mutations characterized by expression in exogenous systems like *Xenopus* oocytes or transfected mammalian cell lines. Table 1 summarizes all of the NSHL (in black) and syndromic deafness (red) associated mutations that have been functionally tested in this fashion. Some variability in results have been reported by different labs, perhaps because of different expression systems, different modes of characterization or perhaps even variation in expression levels. In these cases, we have reported the result which shows the higher level of function (e.g. formation of junctional plaques over no gap junction formation).

Based on frequency of mutated residues (shown at the bottom of Table 1), M2 shows the highest density of mutations associated with NSHL (67%), followed by M3 (50%), E2 (43%), M4 (40%), NT, CL (36%), M1 and E1 (33%). When the frequency of mutagenesis leading to all

Download English Version:

https://daneshyari.com/en/article/10797102

Download Persian Version:

https://daneshyari.com/article/10797102

Daneshyari.com