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Forum Review Article

Connexin-Caused Genetic Diseases and Corresponding Mouse Models

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Abstract

The human and mouse genomes contain 21 and 20 connexin genes, respectively. During the last 10-year period, genetic research on connexins has been stimulated by two parallel approaches: first, the characterization of genetic diseases that are caused by connexin mutations and, second, the generation and characterization of connexin knockout (null) mutated mice in which the coding region of nearly all connexin genes has been deleted. We summarize the current results of each of these two approaches. More recently, first results have been published in which connexin point mutations in human connexin genes were inserted at the corresponding position of the orthologous mouse gene. Under these conditions, the mutated connexin protein is expressed, in contrast to a connexin null mutation, and its interaction with other connexin isoforms or other connexin-binding proteins can be maintained. In this review, we discuss advantages and problems of such an approach and possible implications regarding the mechanism of the disease. The long-term goal is to understand the biologic function of each connexin isoform and the contribution of these proteins to the physiology of the corresponding organs in health and disease. *Antioxid. Redox Signal.* 11, 283–295.

Introduction

GAP JUNCTIONS are intercellular conduits formed between adjacent cells, allowing direct metabolic and electrical coupling of contacting cells by diffusional exchange of metabolites, ions, and second messengers up to 1.8 kDa in molecular mass (67, 106). Each cell contributes a hemichannel (or connexon) composed of six protein subunits, termed connexins. Until now, 21 human and 20 mouse connexin genes have been described (92), coding for transmembrane proteins that share the same domain structure. Connexin proteins consist of four transmembrane domains, two disulfide-stabilized extracellular loops, amino- and carboxy-terminal regions, and a cytoplasmic loop.

Recently, the nomenclature of the human (http://www.genenames.org/genefamily/gj.php) and mouse connexin genes (http://www.informatics.jax.org/) has been revised and will be used in this form throughout this article. The members of the connexin gene family are cell type–specifically expressed and can assemble into homomeric or, when two or more isoforms are expressed in the same cell, into heteromeric connexons forming homo- or heterotypic channels (19). These channels differ from each other by their unitary conductance (76), permeability (74), and regulation (35), maintaining proper embryonic development and sustaining tissue function in the adult organism. In addition, connexin hemichannels have been discussed to play important roles in paracrine signaling (94) and cardiac function (11) (Fig. 1). Mutations in connexin genes lead to alterations in important biologic functions of gap-junction channels and hemichannels, disturbing intercellular communication (51) and/or modifying hemichannel activity (17, 50), thus causing and aggravating symptoms of hereditary human disorders. These diseases (Table 1) can be divided into seven major classes: neuropathic or myelin disorders, nonsyndromic and syndromic deafness, skin diseases, cataracts, oculodentodigital dysplasia, and idiopathic atrial fibrillation.

Connexin Diseases and Mouse Models

Connexin32 (Cx32) mutations were first described to be associated with the X-linked Charcot-Marie-Tooth disease (7). Currently, >270 mutations in the Cx32 gene are known to cause this disease. The second neuropathic connexin disorder is the Pelizaeus-Merzbacher–like disease, caused by nine known recessive mutations in the Cx47 gene (10, 86, 98, 107). Nonsyndromic deafness is the most frequent phenotype of connexin-linked diseases with mutations in Cx26, Cx30, or Cx31 (http://davinci.crg.es/deafness/index.php). In addition, some mutations in Cx26 and Cx31 lead to syn-

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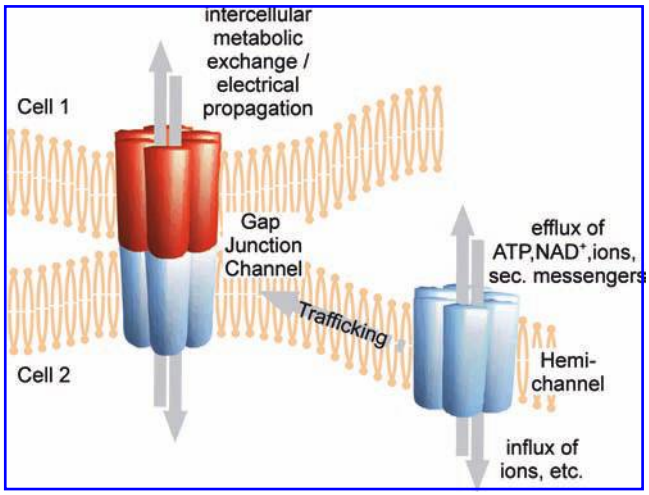

FIG. 1. Proposed functions of gap-junction channels and hemichannels. Gap junctions mediate intercellular communication by allowing exchange of small molecules like metabolites or second messengers up to 1.8-kDa molecular mass. Connexons or hemichannels on their way to a gap-junction plaque can open transiently, mediating efflux of ATP, NAD^+, ions, or second messengers and influx of Ca^{2+} and other ions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars)

dromic deafness [*i.e.*, deafness accompanied by skin disorders like palmoplantar keratoderma (80, 99) and palmoplantar hyperkeratosis (36), mutilating keratoderma (Vohwinkel syndrome) (62), keratitis and ichthyosis (KID) (81), or erythrokeratodermia variabilis (EKV) (56)]. The associated skin disorders also occur alone, leading to hidrotic ectodermal dysplasia (Clouston syndrome) (52) and EKV as a result of Cx30, Cx30.3, or Cx31 mutations (59, 80). Pathologic mutations of connexins in the lens (Cx46 and Cx50) are among the genetic reasons for the development of zonular pulverulent cataracts (60, 89), whereas mutations in Cx43, which is expressed in many cell types, cause the rare oculodentodigital dysplasia (ODDD). More than 30 mutations, including point mutations, codon duplications, and a frame shift in the Cx43 coding DNA, were reported to lead to the pleiotropic phenotype of ODDD (71). A new link between human diseases and connexins has recently been reported. Gollob *et al.* (28) described four mutations in Cx40 gene causing idiopathic atrial fibrillation, thereby underlining the importance of gap-junctional function in cardiac physiology. During the last 20 years, the generation of many connexin mouse models that lack the coding region (null mutated mice) or express a point-mutated connexin gene provided important mechanistic insights into understanding the molecular biology of human disorders. In this review, we discuss the strengths and problems of these approaches by comparing the human and mouse phenotypes and suggest improvements of the corresponding mouse models.

Myelin Disorders: *GJB1* (Cx32) and *GJC2* (Cx47) Mutations Lead to X-linked Charcot-Marie-Tooth (CMTX) and Pelizeus-Merzbacher-Like Disease (PMLD1)

X-linked Charcot-Marie-Tooth (CMTX) disease is caused by mutations in the *GJB1* gene (Cx32) on chromosome Xq13.1 and was the first described connexin-linked human disorder. CMTX is clinically manifested by limb weakness and progressive demyelination of peripheral axons (7). Because of x-linked inheritance of the mutated GJB1 allele, CMTX males tend to be more severely affected than the females, whereas in some cases, late severe symptoms have been described. Thus, the dominance of this disease is variable.

In comparison to the CMTX phenotype in the human, Cx32-null mutated mice express a late-onset neuropathy, underlining the important role of gap-junctional communication for maintenance of the peripheral myelin (4). Abnormal thin myelin sheets and a slight decrease in nerve coupling were frequently described, thus representing an animal model of CMTX. However, the behavior of Cx32-null mutated mice appears to be similar to that of wild-type mice and thus is different from the human CMTX phenotype. These differences in human and mouse phenotypes could be due to anatomic differences of myelinated tissue. The length of the neuronal fibers and the obvious difference of mouse and human susceptibility to impaired conductance properties can be responsible for the less-severe phenotype in Cx32-null mutated mouse compared with CMTX patients.

The second connexin-linked myelin disorder is the Pelizeus-Merzbacher–like disease 1 (PMLD1), which is caused by recessively inherited mutations in the *GJC2* (Cx47) gene (10, 86, 98, 107). PMLD1 patients are characterized by a mild peripheral neuropathy (nystagmus, progressive spasticity, and ataxia) relative to those with Pelizeus-Merzbacher disease (PMD). PMD is associated with mutations in the *PLP1* gene encoding the proteolipid protein 1, the major component of myelin in the CNS. In contrast, the *GJC2* gene is transcribed in humans in the brain and spinal cord at high levels and is less abundant in skeletal muscle, most probably because of a contamination with nerve fibers in the muscle tissue, but not in sciatic and sural nerves (98). In the mouse, Cx47 is expressed in oligodendrocytes in highly myelinated CNS and in few S100β-positive cells (70). Cx47-null mutated mice exhibit slight vacuolation of myelinated nerve fibers without behavioral abnormalities. This vacuolation was much more abundant in mice lacking in addition Cx32, another connexin isoform expressed in oligodendrocytes (double-null mutated mice), leading to action tremors and death on approximately day 51 after birth (66, 70).

Thus, in the mouse, Cx32 appears partially to compensate for the lack of Cx47 in myelinated tissue. The relatively strong symptoms observed in PMLD patients in comparison to Cx47-null mutated mice and the similarity to the Cx32/Cx47 double-null mutated mice suggest that Cx47 mutations could exert a transdominant negative effect onto Cx32. This, however, is in contrast to the recessive inheritance of the PMLD phenotype. Possibly other mechanisms like increased hemichannel activity, as already described for some Cx32 mutations (1, 53), might be responsible for the observed neuropathy in PMLD.

Nonsyndromic and Syndromic Deafness: *GJB2* (Cx26), *GJB3* (Cx31), *GJB6* (Cx30), and *GJA1* (Cx43) Mutations

Sensorineural hearing loss alone (nonsyndromic deafness) or accompanied by hyperproliferative skin disorders (syndromic deafness) in humans have clearly been linked to mu-

TABLE 1. HUMAN AND MOUSE CONNEXIN GENES, CORRESPONDING HUMAN DISEASE, AND PHENOTYPIC ALTERATIONS IN NULL-MUTATED MICE

Human connexin gene protein	*Human disease*	*Mouse connexin gene protein*	*Phenotype of connexin-null mutated mouse*
GJA1 Cx43	Oculodentodigital dysplasia (ODDD)	Gja1 Cx43	Cardiac dysmorphogenesis (postnatal lethality)
GJA3 Cx46	Zonular pulverulent cataract-3 (CZP3)	Gja3 Cx46	Zonular nuclear cataracts
GJA4 Cx37	Predisposition to arteriosclerosis	Gja4 Cx37	Female sterility
GJA5 Cx40	Idiopathic atrial fibrillation	Gja5 Cx40	Atrial arrhythmias
GJA6P —	—	Gja6 Cx33	—
GJA8 Cx50	Zonular pulverulent cataract-1 (CZP1)	Gja8 Cx50	Microphthalmia, congenital cataracts
GJA9 Cx59	—	—	—
GJA10 Cx62	—	Gja10 Cx57	Coupling deficiency in horizontal cells
GJB1 Cx32	X-linked Charcot-Marie-Tooth disease (CMTX)	Gjb1 Cx32	Late-onset progressive neuropathy, decreased glycogen degradation, increased liver carcinogenesis
GJB2 Cx26	Nonsyndromic and syndromic deafness, palmoplantar hyperkeratosis, keratitis-ichthyosis deafness (KID), Vohwinkel syndrome	Gjb2 Cx26	Lethality at ED 11
GJB3 Cx31	Nonsyndromic and syndromic deafness, erythrokeratodermia variabilis (EKV)	Gjb3 Cx31	Transient placental dysmorphogenesis
GJB4 Cx30.3	Erythrokeratodermia variabilis (EKV)	Gjb4 Cx30.3	Reduced behavioral response to a vanilla scent, no hearing anomalies
GJB5 Cx31.1	—	Gjb5 Cx31.1	Impaired placental development
GJB6 Cx30	Nonsyndromic deafness, hydrotic ectodermal dysplasia (Clouston syndrome)	Gjb6 Cx30	Hearing insufficiency, no skin phenotype
GJB7 Cx25	—	— —	—
GJC1 Cx45	—	Gjc1 Cx45	Lethality at ED 10.5
GJC2 Cx47	Pelizaeus-Merzbacher-like disease 1	Gjc2 Cx47	Vacuolation of nerve fibers
GJC3 Cx30.2	—	Gjc3 Cx29	Development of hearing (?)
GJD2 Cx36	Predisposition to juvenile myoclonic epilepsy	Gjd2 Cx36	Night blindness
GJD3 Cx31.9	—	Gjd3 Cx30.2	Increased atrioventricular conduction velocity
GJD4 Cx40.1	—	Gjd4 Cx39	—
GJE1 Cx23	—	Gje1 Cx23	—

tations in three β-group connexin genes: *GJB2* (Cx26), *GJB3* (Cx31), and *GJB6* (Cx30). Moreover, mutations in the *GJA1* gene (coding for the Cx43 protein) were found in patients with nonsyndromic autosomal recessive and sensorineural deafness (26, 54, 112). In addition, mutations in *GJA1* pseudogene (*GJA1P1*) have been reported (112). The cause for deafness in these patients could also be mutations in one of >100 genes responsible for nonsyndromic deafness. More than 50% of all cases of prelingual nonsyndromic deafness can be linked to Cx26 mutations. In contrast, mutations in other disease-causing genes were rarely described in deaf patients and thus seem to be less frequent than Cx26 mutations in auditory pathology (72). Nonsyndromic deafness can be inherited in an autosomal dominant (DFNA) or recessive (DFNB) manner, whereby recessive forms are usually more severe because of cochlear defects. Conspicuously, 35delG is

the most frequent deafness-causing Cx26 mutation in white populations and was detected at higher frequency than the major deltaF508 mutation of the *CFTR* gene, causing cystic fibrosis in the southern Europe and Mediterranean regions (20, 57). The 35delG mutation consists of a deletion of one of six guanine residues (G) at the positions 30 to 35, leading to a premature stop at position 38 and a strongly truncated Cx26 protein. Thus, the 35delG mutation is similar to Cx26 functional deficiency.

With Cx26-null mutated or point-mutated mice, it was suggested that this protein might be necessary for K^+ recycling and Ins(1,4,5)P_3 passage, which is important for Ca^{2+} wave propagation in the inner ear (9, 12, 49). The tissue-specific ablation of Cx26 in the inner ear by using the Otogenin-Cre mice as well as the transgenic loss-of-function Cx26 R75W mutation lead to apoptosis of hair cells followed by deafness. Thus, the role of Cx26 in keeping the endolymphatic potassium concentration at high levels is fundamental in hearing. Cx30 and Cx43 (at low levels) are co-expressed with Cx26 in supporting cells in the cochlea, suggesting that these isoforms can also play a role in K^+ recycling (108). Originally, the Cx30 function appeared to be crucial for hearing in the mouse. Connexin30-null mutated mice showed constitutive hearing impairment because of a lack of the electrical-potential difference between the endolymphatic and perilymphatic compartments and/or apoptosis of auditory hair cells (96). Recently, however, the hearing impairment in $Cx30^{-/-}$ mice could be rescued by overexpression of Cx26, resulting in the prevention of hair-cell death (3). Thus, not the specific loss of Cx30 but the reduction of the total level of GJC appears to lead to apoptosis of hair cells (75).

In contrast, the function of Cx31, which is also expressed in the human cochlea and whose mutations in humans also lead to hearing impairment, is not clear. Cx31 is expressed in fibrocytes of the spiral ligament and the spiral limbus of the mouse cochlea (109), but its absence does not impair hearing (73). This difference between human and mouse could be due to observed channel properties between the two species [*i.e.*, in contrast to mouse Cx31, human Cx31 (hCx31) can form functional heterotypic channels with Cx26, Cx30, Cx32, and Cx45 in HeLa cells (2)]. The interaction of hCx31 with Cx26 and Cx30, which are coexpressed in the cochlea, could be the link for Cx31 function in K^+ recycling, possibly by disturbing the coupling of the other connexin isoforms.

In contrast to nonsyndromic deafness, syndromic deafness includes additional skin disorders besides the hearing insufficiency, such as palmoplantar keratoderma (PKK), ectodermal dysplasia keratitis-ichthyosis deafness (KID), hystix-like ichthyosis deafness (HID), Vohwinkel syndrome, Bart-Pumphrey syndrome, and erythrokeratodermia variabilis (EKV) (82, 100). The majority of these diseases are linked to Cx26. Only deafness associated with EKV is caused by Cx31 mutations (56), whose clinical features as well as their corresponding mouse models are discussed in the next section.

In contrast to nonsyndromic deafness caused by Cx26 mutations, only a few mutations lead to deafness and skin disorders in the same patient (82, 100). Noticeably, all known mutations causing both phenotypes are localized within the first third of the Cx26 protein. This raises the speculation that these first protein domains could be responsible for interaction with another Cx26 protein and other connexin isoforms coexpressed in the epidermis (51). This assumption seems to be supported by the Cx26 R75W mutation, which exhibits a transdominant effect onto Cx43 in *Xenopus* oocytes (51). The dominant Cx26 R75W protein in mice does not lead to an alteration in skin morphology or differentiation (49), but to PKK, besides deafness in humans. However, the Cx26 D66H mutation driven by the keratin 10 (K10) promoter causes, in the mouse, phenotypic abnormalities similar to Vohwinkel syndrome, thus providing a model for this human disorder (5). Thereby, this mutation was able transdominantly to inhibit the wild-type Cx26 and Cx43 functions (97). The reason that one mouse mutant only poorly reflects the human symptoms, whereas the other can do better, is not yet known. However, both mouse models (R75W and D66H mutants) (Table 2) have some disadvantage: unequal expression of the mutated to the wild-type protein. Overexpression of the mutated connexin could lead to problems in protein turnover (51) and thus to a weaker or stronger phenotype in the mouse compared with the corresponding patients.

Skin Diseases: *GJB6* (Cx30), *GJB4* (Cx30.3), and *GJB3* (Cx31) Mutations

The human connexin skin disorders not associated with deafness are erythrokeratodermia variabilis (EKV) and Clouston syndrome. These two diseases are caused by dominant mutations in genes coding for Cx31 (79) and Cx30.3 (59) or Cx30 (52), respectively. The symptoms of EKV patients become obvious during childhood because of slowly growing erythematous patches that have a tendency to be limited to the trunk. Furthermore, static keratodermas can occur. Cx30 mutations lead in humans to Clouston syndrome, a disorder with a highly variable phenotype, such as the occurrence of hypotrichosis, palmoplanar keratoderma, nail dystrophy, or hyperpigmentation. The reason for the strong variability and thus the consequences of the connexin mutations are possibly due to a different genetic background in the individual patient (100).

The comparison of the human connexin diseases in the skin with the corresponding mouse models shows that the ubiquitous deletion of Cx31 or Cx30.3 does not affect proper skin differentiation, but a point mutation in Cx31 (Cx31F137L) resembles more the human phenotype (86). Cx31-null mutated mice showed placental defects, like reduced labyrinth and decreased size of spongiotrophoblasts, resulting in loss of more than half of $Cx31^{-/-}$ embryos between ED10.5 and 13.5 (73). Presumably, anatomic differences between the placentae in humans and mice could be the reason that these symptoms are not observed in EKV patients. In contrast, no skin alterations were described for Cx30- or Cx30.3-null mutated mice, although the expression pattern of both connexins is similar to their homologues in humans (Table 3) and cannot be explained by an obvious anatomic difference between the two species. In contrast, the dominant Cx31F137L-mutated mice are viable only in heterozygous state; homozygosity of this mutation is lethal on ED7.5 (86). This comparison shows that the mechanism leading to these human disorders is not due to a simple absence of the corresponding connexin protein. It is possible that mutations in these proteins could develop transdominant effects on other isoform [for example, Cx31 mutations onto Cx43, as discussed in (86)]. An increased hemichannel activity

TABLE 2. HUMAN CONNEXIN-CAUSED DISEASES AND PHENOTYPES OF CONNEXIN POINT-MUTATED AND NULL-MUTATED MICE

Human phenotype	*Connexin point-mutated mouse*	*Connexin-null mutated mouse*
Syndromic deafness		
Cs26R75W		Ubiquitous $Cx26^{-/-}$: embryonically lethal at ED11 due to decreased transplacental uptake of glucose (25)
Syndromic deafness, palmoplantar keratoderma	Nonsyndromic deafness, transgenic knockin driven by CAG promoter (expression in various cell types)	
Cx26D66H		Conditional $Cx26^{OtogCre}$ in inner ear: Cell death of support cells of inner hair cells (12)
Syndromic deafness, Vohwinkel syndrome	Apparent Vohwinkel syndrome, transgenic knockin driven by keratin 10 promoter (selective expression in skin)	
Nonsyndromic deafness, Erythrokeratoderma variabilis (EKV)	Cx31F137L Mild EKV phenotype (85)	$Cx31^{-/-}$ Placental defects, but no alteration in hearing or skin development (72)
Oculodentodigital dysplasia (ODDD)		
Cx43G61S		$Cx43^{-/-}$:
Not described in human	ODDD phenotype Altered cardiac morphology Cardiac arrhythmias (23)	Postnatal lethality caused by failure in pulmonary gas exchange due to morphologic alteration in cardiac outflow tract (76)
Cx43I130T		
Cardiac tachyarrhythmias	Cardiac arrhythmias (41)	Cx43 Cre-ERT/flox Cx43fl/fl; MHC-MLC-Cre
Cx43G138R		Severe cardiac arrhythmias leading to ventricular fibrillation and death (18, 33)
No obvious cardiac phenotype	No alteration in cardiac morphology Cardiac arrhythmias (16)	

TABLE 3. HUMAN AND MOUSE CONNEXIN PROTEINS AND THEIR CORRESPONDING EXPRESSION PATTERN

Human connexin protein	*Major expression in human*	*Mouse connexin protein*	*Major expression in mouse*
Cx43	Many cell types	Cx43	Many cell types
Cx46	Lens	Cx46	Lens
Cx37	Endothelium	Cx37	Endothelium
Cx40	Heart, endothelium	Cx40	Heart, endothelium
—	—	Cx33	—
Cx50	Lens	Cx50	Lens
Cx59*	Testis, skeletal muscle	—	—
Cx62*	Heart, skeletal muscle	Cx57	Retina, thymus
Cx32	Liver, Schwann cells, oligodendrocytes, peripheral and central nervous system	Cx32	Liver, Schwann cells, oligoendrocytes, peripheral and central nervous system
Cx26	Skin, cochlea, liver, placenta	Cx26	Skin, cochlea, liver, placenta
Cx31	Skin, placenta	Cx31	Skin, placenta
Cx30.3	Skin	Cx30.3	Skin, olfactory system
Cx31.1	Skin	Cx31.1	Skin, placenta
Cx30	Skin, brain, cochlea	Cx30	Skin, brain, cochlea
Cx25*	Placenta	—	—
Cx45	Heart, smooth muscle, neurons	Cx45	Heart, smooth muscle, neurons
Cx47	Brain, spinal cord	Cx47	Brain, spinal cord
Cx30.2*	Heart, brain, pancreas, placenta, liver, skeletal muscle, kidney	Cx29	Myelinating cells
Cx36	Neurons	Cx36	Neurons
Cx31.9	—	Cx30.2	Cardiac conduction system, interneurons
Cx40.1*	Pancreas, kidney, skeletal muscle, liver placenta, heart	Cx39	Skeletal muscle
Cx23	—	Cx23	—

Some human connexin genes are differently transcribed compared with their mouse homologues (89; *asterisks*).

causing extracellular leakage of ions and metabolites leading to cell death could be excluded for the Cx31F137L mutation in mouse embryonic stem cells but not in skin. Thus, it is not clear which molecular mechanism causes this human skin disorder.

Cataracts: *GJA3* (Cx46) and *GJA8* (Cx50) Mutations

Mutations in *GJA3* (coding for Cx46) and *GJA8* (coding for Cx50) lead in humans to aberrant gap-junction intercellular communication (GJIC) and development of different forms of lens opacities, also known as cataracts. The observed cataracts in patients with connexin mutations are the dominantly inherited zonular pulverulent cataract type 1 (CZ1), caused by Cx50 mutations (89), and type 3 (CZ3) due to Cx46 mutations (60).

Lens fiber cells are highly specialized. They accumulate soluble crystalline proteins and do not contain their own cell organelles. Thus, they are transparent but depend on the metabolic support by other cells through gap-junction conduits. Generally, three connexin isoforms are expressed in the total lens: *GJA1* (Cx43), *GJA3* (Cx46), and *GJA8* (Cx50), whereas in lens fiber cells, only the last two proteins occur, supporting cell growth, maintaining the homeostasis and thus the transparency (31). Just this aspect could be ascertained by using connexin-null mutated mice. It was shown that Cx46 deficiency in the mouse led to severe cataracts without disturbing lens development and growth (29, 30). The function of Cx50 is mostly limited to the support of the growth of fiber cells (83), which cannot be restored by replacement of the Cx50 coding DNA by that of *GJA3* (Cx46) in a knockin mouse model (Cx50KiCx46) (63). Only mild nuclear cataracts were observed in $Cx50^{-/-}$ mice, supporting the conclusion that this isoform does not excessively mediate intracellular coupling in the lens. The interaction of Cx46 and Cx50 proteins results in functional heteromeric and heterotypic channels in *Xenopus* oocytes (38) and cultured cells (104). The *in vivo* function of the channels was recently described by using a dominant cataractous mouse model expressing the Cx50S50P mutation (110). Xia *et al.* (110) demonstrated that the coexpression of the S50P mutant with wild-type Cx50 inhibited the elongation of primary lens fiber cells, whereas the coexpression of the mutant with wild-type Cx46 inhibited differentiation of secondary fiber cells. In contrast, the function of Cx43 in the lens is not clear. The neonatal lethality in Cx43-null mutated mice might have prevented investigators from determining the long-term function of this protein in the lens. The absence of Cx43 and Cx50, as well as Cx43 alone, did not disturb the development and did not cause cataracts in prenatal lens (105).

However, the development of connexin-linked cataracts also depends on the action of other proteins (*i.e.*, so-called genetic modifiers). It was observed that Cx50 deficiency leads to cataracts of different severity, dependent on the genetic background (27). Recently, the protease calpain 3 was described to play an important role in age-related cataractogenesis in Cx46 mice (95). This observation is consistent with the hypothesis that intracellular Ca^{2+} concentration increases in Cx46-null mutated lens, resulting in an activation of Lp82/85, a calpain 3 isoform, and -crystallin cleavage, an important part of the initiation of cataractogenesis (6).

Further insights into the biology of cataracts can be found in the review article written by V. Berthoud and E. Beyer in the same issue of this journal.

Oculodentodigital Dysplasia (ODDD): *GJA1* (Cx43) Mutations

Connexin43 mutations in human result in autosomal dominantly inherited oculodentodigital dysplasia (ODDD) (71). This pleiotropic developmental disorder shows high penetrance and variable expression (41) because relatively frequent *de novo* mutations (78). ODDD is characterized by ophthalmologic, dental, and craniofacial anomalies as well as alterations in bones and limbs, such as syndactylies (21). A thin nose with hypoplastic alae nasi, mandibular overgrowth with a wide alveolar ridge, and microcephaly lead to the characteristic appearance of most ODDD patients. Furthermore, cleft palate (69), thin sparse or curly hair (45), microcornea, glaucoma, cataracts, and optic atrophy (103), and more rarely, neurologic (lalopathy, bladder disturbances, paraparesis, ataxia, and leukodystrophy) (8, 55) and cardiac (arrhythmia) (71) problems have been described for ODDD patients.

Currently, >30 mutations in the *GJA1* gene are known to cause ODDD, but only one frameshift mutation in the carboxy-terminal part of Cx43 has been described, leading to a premature stop and a truncation of the protein. Patients carrying this mutation develop palmoplantar keratoderma (101). Morphologic alterations of the skin and a defect of the epidermal water barrier have been observed in Cx43K258stop mouse mutants lacking the last 125 amino acid residues of the carboxy-terminal region of Cx43 (58). Although striking differences like the absence of dominance of the Cx43K258stop mutation or the dissimilarity of the skin phenotypes are obvious between the two species, both mutations in human and mice confirm the transspecies importance of the carboxy-terminal Cx43 region. Many phosphorylation and protein-binding sites are located in this region. Their loss in mice results frequently in lethality shortly after birth (58).

Most ODDD-associated mutations are point mutations leading to amino acid exchanges within the first half of the protein. Some of the mutations, like Y17S, G21R, I31M, A40V, F52dup, L90V, I130T, K134E, G138R, G143S, R202H (17, 50, 84, 87, 88), have been functionally analyzed regarding GJIC and hemichannel activity in cultured cells. All tested mutations disturbed dominantly Cx43-mediated coupling but differently affected the hemichannel activity. Thus, loss-of-function (Y17S, G21R, A40V, F52dup, L90V, and I130T) (50) and gain-of-function (I31M, G138R, and G143S) (17) mutations have been identified. Some of the mutations associated with neurologic abnormalities lead to hemichannel dysfunction (Y17S, L90V, and I130T) or increase in their activity (G138R). However, the physiologic functions of hemichannels or even their identity have not been clarified (93). It is not clear whether the disturbed hemichannel activity is responsible for these symptoms. Recently, we showed that the increased hemichannel activity in the Cx43G138R mutated mice leads to an aggravation of their cardiac phenotype, especially after hypoxic stimulation (16).

Cx43-null mutated mice are dead shortly after birth and thus cannot be used as mouse models for ODDD. Thus, mice carrying point mutations in the *GJA1* gene have been developed. Three mouse models were generated, showing an ODDD-like phenotypes, the Cx43G61S (23), Cx43G138R (16), and Cx43I130T (42)-expressing mice (Table 2). Besides the development of diverse ODDD characteristics, striking car-

diac phenotypes are present in all models, although for only one of the three mutations, the I130T, were cardiac arrhythmias were described in the corresponding patients (71). Unfortunately, it is uncertain whether the cardiac phenotype in Cx43I130T-expressing mice is specific for this mutation or shares a mechanism similar to the other two mutations also leading to arrhythmias. In humans, ODDD-associated cardiac symptoms are relatively rare. This discrepancy between humans and mice could be explained by intra- and interfamilial variability, as already seen in other symptoms of ODDD-like syndactylies (14). The individual genetic background in each patient could be responsible for the variability. This aspect has already been proposed for the high variability in symptoms of Clouston syndrome caused by Cx30 mutations (100) or cataractogenesis in Cx50-null mutated mice (27). Thus, variability between the different ODDD mouse models regarding the cardiac phenotype does not occur, because they have a similar genetic background. It is difficult to predict a potential genetic modifier altering the severity or appearance of cardiac arrhythmia in ODDD, as already described for calpain 3 in cataractogenesis (6). However, recently the *KCNJ2* gene coding for Kir2.1, a K^+ channel subunit protein important for the maintenance of resting potential in cardiomyocytes, has been described to be closely regulated with Cx43 by the microRNA miR-1 (111). Until now, however, a defined connection between ODDD-associated cardiac symptoms and the *KCNJ2* gene expression has not been reported.

A possible explanation for the interfamilial variability could also be the functional differences between the single mutations. Recently, a different potency of the G21R and G138R mutations has been described: the G21R-mutated Cx43 is twice as potent in inhibiting the wild-type Cx43 function as the G138R-mutant protein (31).

For Cx43, the best-described member of the connexin gene family, the complexity of connexin mutations is evident. The phenotypes of Cx43 mutations that can disturb GJIC, alter hemichannel function, and disrupt its regulation or protein interaction clearly differ from a complete deletion of the Cx43 gene (Fig. 2A).

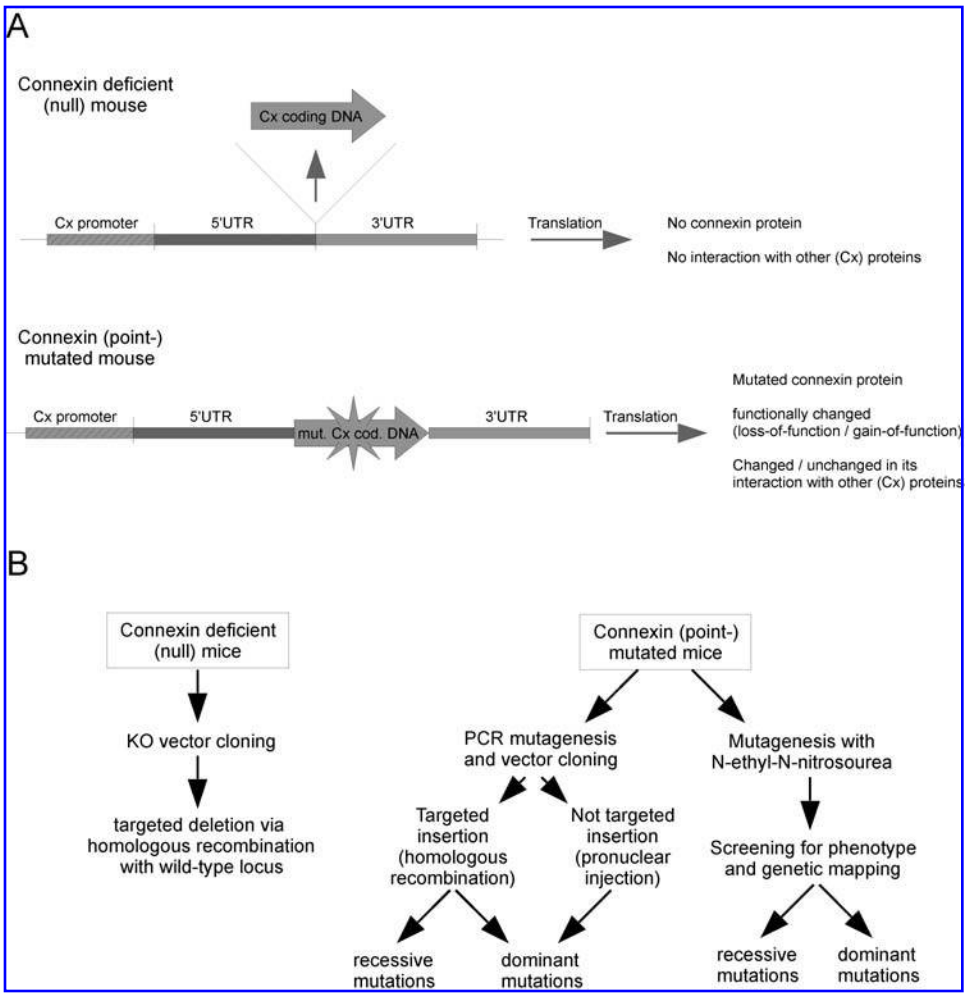

FIG. 2. Basic differences between connexin null-mutated and point-mutated mouse models. (**A**) In null mice, the coding region for a connexin protein has been deleted from its genomic locus. Lack of the connexin gene and consequently of its protein leads to absence of native function and interaction with other connexin and nonconnexin proteins. In connexin point-mutated mice, the modified coding sequence is present in the genome and can be translated to a mutated protein. Then the function of this connexin protein, as well as its interaction with other proteins, can be altered. (**B**) Strategies for the generation of connexin mouse mutants. Connexin-deficient (null) mice lack the targeted Cx coding DNA after homologous recombination of the cloned knockout (KO) vector with the wild-type gene locus (nonconditional approach; **left**), whereas the generation of Cx (point-) mutated mice can be achieved in many ways (**right**). To express a distinct mutation, a vector containing the (PCR) mutated gene can be inserted into the genome *via* homologous recombination (targeted approach) or pronuclear injection (untargeted approach). Because of a randomized insertion after a pronuclear injection and persistent expression of the wild-type gene, only effects of dominant mutations can be studied with this approach. Random mutagenesis (for example, by treatment of male mice with *N*-ethyl-*N*-nitrosourea and subsequent mating with untreated females) can also generate new gene mutations after phenotypic screening and genetic mapping. However, this strategy does not offer the possibility of generating a specific point-mutation.

Idiopathic Atrial Fibrillation: *GJA5* (Cx40) Mutations

Recently, mutations in *GJA5* gene, coding for Cx40, have been described in patients with idiopathic atrial fibrillation (28). Lymphocytic blood and cardiac tissue samples were analyzed with PCR amplification and sequencing of the *GJA5* gene. Besides one obvious polymorphism (M163S), three mutations (P88S, G38D, and A96S) in Cx40 were detected in four of 15 patients with idiopathic atrial fibrillation. Notably, two of the ascertained mutations were somatic (*i.e.*, they originated and were expressed only in the heart, but could not be found in lymphocytic DNA). The Cx40 A96S mutation was genetically inherited. The same publication (28) described functional disturbances of these mutations regarding trafficking, gap-junctional coupling in *Xenopus* oocytes, and their influence on wild-type Cx40 and Cx43 function. The mutations (P88S and G38D) defective in intracellular protein trafficking as well as the plaque-forming mutation (A96S) clearly showed a reduction in intercellular communication, dominance on wild-type Cx40, and transdominance on wild-type Cx43–mediated electrical coupling. These findings suggest that the strong reduction of gap junction–mediated cellular communication in the heart causes the atrial fibrillation observed.

Others described the predisposition to atrial arrhythmia in patients carrying specific polymorphisms in the promoter region of Cx40 (32), which led to attenuated activity of this regulatory element and decreased Cx40 expression (40).

Similar to these reports, Simon *et al*. (90) as well as Kirchhoff *et al*. (43, 44) demonstrated the importance of Cx40- and Cx43-mediated intercellular communication in normal heart physiology. Cx40 deficiency in the mouse led to a disturbance of intercellular communication in the atrium and conduction system, as shown in a prolongation of the atrial and ventricular ECG parameters and atrial arrhythmia (43). Furthermore, $Cx40^{+/-}/Cx43^{+/-}$ mice also exhibited alterations in ventricular conduction (44). Thus, the results obtained from these mouse mutants widely seem to reflect the situation in human patients. Both the human Cx40 mutations and the Cx40 deficiency in mouse disturb the proper impulse propagation in the heart, generating an arrhythmic substrate because of loss of gap-junctional coupling.

However, another, very recently described aspect, is the Cx40 expression in the kidney and its influence on blood-pressure control by the renin–angiotensin system (102). Cx40-null mutated mice are hypertensive, possibly due to an increase in the number of renin-secreting cells (46) and a loss of the Cx40-mediated calcium-dependent inhibitory effect of angiotensin II and intrarenal pressure (102).

It is unclear, however, whether the Cx40 mutations found in humans lead to an increase of blood pressure or act only in the heart, although alterations in Cx40 expression are accompanied by an increase of systolic blood pressure (22, 40). The increase of blood pressure due to alterations in Cx40 expression or function could initiate atrial fibrillation in these patients. Additional examination of patients and the generation of Cx40-mutated mouse models may help to unravel the mechanisms leading to Cx40-associated idiopathic atrial fibrillation.

Outlook

The direct comparison of the connexin-caused human diseases with their symptoms in the corresponding transgenic mice described so far shows that only some mouse models developed symptoms similar to those of humans. Most of the reported mouse mutants are connexin-null mutated (*i.e.*, lack the corresponding coding DNA). Thus, the dissimilarity of symptoms in humans and mice could be due to mechanistic differences between connexin absence and point mutations. In connexin-null mutated mice, the coding region/s are missing, so that the corresponding gene is not expressed, whereas in connexin point-mutated mice, the mutated protein is translated. This can lead to alterations of GJIC and hemichannel function or interaction with diverse interaction partners like other connexin isoforms or other binding proteins (Fig. 2A). Thus, the transdominant effect of many mutations in different connexin genes, like Cx26R75W or Cx40P88S, Cx40G38D and Cx40A96S on another family member, Cx30 or Cx43, respectively, was not observed in null-mutated mice.

However, because of differences in connexin-expression pattern (Table 3) or anatomy between humans and mice, the phenotypes of connexin-mutated mice can differ from human symptoms. In Cx31F137L mice, the lack of erythemas may be due to the dense fur. Another dissimilarity between the two species concerns all reported ODDD mouse models so far. All of them develop striking cardiac arrhythmias, although cardiac problems are very rare in patients with ODDD. The difference between arrhythmias observed in ODDD-mutated mice but not in ODDD patients is currently still difficult to explain, but could be due to the similar genetic background in the mice and the genetic differences between ODDD patients. Thus, the development of cardiac arrhythmias in ODDD patients could be due to the interplay of diverse hypothetic genes, so-called modifier genes, which may be important for cardiac physiology. This assumption can be checked by expression of ODDD mutations in different mouse strains of different genetic backgrounds and investigations of the severity and occurrence of arrhythmic events. The genetic background can play an important role in connexin genetics, as previously shown with $Cx46^{-/-}$ or $Cx50^{-/-}$ mice (27). Here, during development of cataracts, calpain 3 is a genetic modifier that can cleave and precipitate -crystallin, leading to lens turbidity after activation by increased Ca^{2+} concentration in $Cx46^{-/-}$ mice (6).

The generation of many mouse models during the last 20 years yielded new mechanistic insights into the importance of connexins for general physiology (different strategies for the generation of connexin mouse mutants are summarized in Fig. 2B). Thus, for instance, Cx40-null mutated mice showed that an obvious loss of intercellular communication and not only defects in ion channel activity can lead to cardiac arrhythmias (43). Later, cardiac arrhythmias were reported in cardiac-specific or -inducible Cx43 mouse mutants (18, 34) or in patients carrying Cx43 (71) or Cx40 (28) mutations.

Surprisingly, neither severe phenotypic alterations in mice lacking neuronally expressed connexin isoforms nor mutations in homologous human genes have been reported. For example, mice deficient in Cx36 (13, 15, 33, 39) or Cx30.2 (47) expression are not phenotypically conspicuous, in contrast to mice null-mutated in Cx47 and Cx32, which are both expressed in oligodendrocytes (66, 70). The consequences of a specific deletion of Cx45 in neurons are not yet fully explored; however, the lethality in Cx45-null mutated embryos

is due to its expression in vessels or the heart but not the brain (48, 65, 68). The lack of severe neuronal phenotypes in $Cx36^{-/-}$ or $30.2^{-/-}$ mice may lead to the assumption that GJIC in neurons may not be essential or could be compensated for by other channels. Consequently, human mutations in these connexin genes may lead to an inconspicuous appearance. Recently, however, some haplotypes of Cx36 could be associated with some cases of juvenile myoclonic epilepsy, a common form of idiopathic epilepsy (37, 64). Furthermore, defects in Cx36 or other connexins expressed in neurons or astroglia may lead to defects in inhibitory networks in the human brain (13), including the consolidation of memory (24). Obviously, many more studies on transgenic mice and human patients are required to dissect the pathologic consequences of connexin defects in the brain.

In the future, therapeutic strategies may be directly tested *in vivo* by using connexin-defective mouse models. Recently, Ahmad *et al.* (3) suggested to increase Cx26 expression or slow degradation of Cx26 protein in Cx30-null mutated, deaf patients to restore GJIC and prevent hearing impairment. The exogenous delivery of Cx26-coding DNA into the inner ear of mice has already been reported (61). Toxicologic and pharmacologic research could take advantage of the available connexin mouse models. Possible side effects and specificity of substances acting on connexins (for example, GJ blockers) must be clarified.

So far, connexin-null mutated mice can mimic only some symptoms of the corresponding human diseases, and the repertoire of point mutations in human connexins has been barely exploited for the generation of new transgenic mice. It can be expected that additional connexin point-mutated mice can yield many new insights into the molecular mechanisms leading to connexin-caused inherited diseases.

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Abbreviations

CMTX, X-linked Charcot-Marie-Tooth; Cx, connexin; CZ1, zonular pulverulent cataract type 1; DFNA, autosomal dominantly inherited nonsyndromic deafness; DFNB, autosomal recessively inherited nonsyndromic deafness; EKV, erythrokeratodermia variabilis; HID, hystix-like-ichthyosis deafness; K10, keratin 10; KID, keratitis and ichthyosis; ODDD, oculodentodigital dysplasia; PKK, palmoplantar keratoderma; PMD, Pelizeus-Merzbacher disease; PMLD1, Pelizeus-Merzbacher–like disease 1.

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