Published in final edited form as:
Arch Biochem Biophys. 2012 August 1; 524(1): 2–15. doi:10.1016/j.abb.2012.03.008.

Biological Role of Connexin Intercellular Channels and Hemichannels

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Abstract

Gap Junctions (GJ) and hemichannels (HC) formed from the protein subunits called connexins are transmembrane conduits for the exchange of small molecules and ions. Connexins and another group of HC-forming proteins, pannexins comprise the two families of transmembrane proteins ubiquitously distributed in vertebrates. Most cell types express more than one connexin or pannexin. While connexin expression and channel activity may vary as a function of physiological and pathological states of the cell and tissue, only a few studies suggest the involvement of pannexin HC in acquired pathological conditions. Importantly, genetic mutations in connexin appear to interfere with GJ and HC function which results in several diseases. Thus connexins could serve as potential drug target for therapeutic intervention. Growing evidence suggests that diseases resulting from HC dysfunction might open a new direction for development of specific HC reagents. This review provides a comprehensive overview of the current studies of GJ and HC formed by connexins and pannexins in various tissue and organ systems including heart, central nervous system, kidney, mammary glands, ovary, testis, lens, retina, inner ear, bone, cartilage, lung and liver. In addition, present knowledge of the role of GJ and HC in cell cycle progression, carcinogenesis and stem cell development is also discussed.

Introduction

Intercellular communication allows the coordination of multiple cellular processes and these communications are in part mediated by low-resistance intercellular channels, the GJ (1). GJ is a transmembrane channel that connects cytoplasm of adjacent cells and is formed by head-to-head docking of connexons or HC, which is formed by hexameric oligomers of transmembrane proteins, the connexins. These proteins expanded by gene duplication into a 21 gene members in human and 20 members in rodent (2). Gap junction intercellular communication (GJIC) and HC regulate signaling and function of various organ systems including central nervous system (CNS), heart, lens, liver, lung, retina, ear, kidney, testis, ovary, breast, bone, skin, etc. (3–8). Most organ systems and cells express different types of connexins, which may oligomerize into homomeric (consisting of only one type of connexin) or heteromeric (formed by a mixture of different connexin isoforms) connexons. Furthermore, these connexons may dock with an identical connexon to form a homotypic or

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a different connexon to form a heterotypic channel. There is evidence for at least some types of connexin channels to be permeable to virtually all soluble second messengers, amino acids, nucleotides, calcium ions, glucose and its metabolites (9), oligonucleotides (short small interfering (si) RNAs) and peptides up to 10 amino acids (10;11). In contrast to the GJ, HC shows low open probability and/or low membrane permeability to small molecules (e.g., ATP, NAD^+, prostaglandins and small fluorescent dyes) in cultured cells under "resting" conditions (12). These channels have been implicated in autocrine/paracrine signaling to provide a pathway for release of ATP (13), glutamate (14), NAD^+ (15) and prostaglandins (16). The roles of connexins, gap junctions and hemichannels are summarized in Fig. 1.

Connexin mutations have been identified in several human diseases, such as mutations in Cx32 giving rise to a common peripheral demyelinating condition, the X-linked Charcot–Marie–Tooth syndrome (17); Cx26 mutations in more than half of hereditary deafness and skin disorders (18;19); Cx47 mutations in a central demyelinating condition called Pelizaeus-Merzbacher-like disease (20); Cx46 or Cx50 mutations in familial cataracts (21;22); and Cx43 mutations underlying the occulodentodigital dysplasia (ODDD) (23). Some of these mutations lead to complete loss of functional channels, while others form functional channels with varying channel properties when compared to the wild type connexin-composed channels (24). In this review, we provide a general overview of GJ, HC, connexins and pannexins in various tissues and organ systems, and their roles in cell growth and differentiation, cell cycle regulation, carcinogenesis and stem cell function.

Another family of GJ proteins identified about a decade ago is the pannexins (25). Mammalian pannexins include three homologous proteins, termed pannexin (Panx) 1, Panx2 and Panx3. Although the detailed structural and functional characteristics of the pannexins remain largely unknown, recent reports show that pannexin-based HC could participate in physiological and pathological events (26–28).

1. Connexins, Gap Junctions and Hemichannels in Various Organs and Tissues

Heart

GJ in heart mainly contains three different connexins, Cx40, Cx43 and Cx45; however, Cx43 is the predominant one. Cx43 is expressed in characteristic combination with the other two connexins in a chamber-related and myocyte-type manner (29;30). The ventricular myocytes mainly contain Cx43-formed GJ, whereas the GJ in the atrial myocytes contains both Cx43 and Cx40 (31). In comparison to Cx43 and Cx40, Cx45 is expressed in low quantities with higher expression in the atria compared to the ventricle (30). The role of GJ in cardiac morphogenesis is revealed by the cardiac malformations in the connexin knockout mice (32–36). Mutations in the carboxyl terminal phosphorylation sites in Cx43 are also shown to cause complex cardiac malformations visceroatria heterotaxia (37) and hypoplastic left heart syndrome (38). Further studies fail to find Cx43 gene mutations in patients with human autosomal recessive lateralization defects (39) and with sporadic and familial heterotaxy (40). GJ is implicated in the spread of molecular signals of ischemia-reperfusion injury among myocytes resulting in rigor contracture and cell death (41;42). Ischemic preconditioning is shown to result in trafficking of Cx43 to the mitochondria (43) and the benefit of preconditioning on infarct size is shown to be abolished in Cx43 heterozygous knockout mice (44), suggesting critical contribution of this connexin to cardiac remodeling following preconditioning. In contrast another report suggests that these mice have smaller infarct size following coronary occlusion (45). These contradicting results could have been due to measurement of infarct size at different time points. Though ischemic preconditioning

prevents ischemia induced Cx43 dephosphorylation, which leads to increased open probability of these channels, the underlying mechanism is still not known. Totzeck et al reported that interaction of phosphatases with Cx43 is not affected during ischemic preconditioning, thus ruling out the contribution of phosphatases in preventing ischemia induced dephosphorylation of this connexin (46). In the cardiomyocytes, Cx43 is shown to be present only in the subsarcolemmal mitochondria but not in the interfibrillar mitochondria (47). Since mitochondrial Cx43 plays a critical role in mediating cardioprotective function of ischemic preconditioning, subsarcolemmal and interfibrillar mitochondia likely differ in transmitting the signals of ischemic preconditioning. Mass spectrometric approach of purified mitochondrial preparation confirms the presence of Cx43 in the mouse myocardium (48). This study further reveals that Cx43 hexamers are present on mitochondrial membranes and this connexin contributes to the mitochondrial K^+ uptake. Rottlaender et al (2010) (47) demonstrate that in mouse cardiomyocytes, Cx43 in the mitochondria provides cytoprotection by stimulating mitochondrial K_{ATP} channels, which play a critical role in conferring protection against ischemic cell injury (49;50). Further support for role of GJ in cardiac function comes from findings showing increased susceptibility of mice to lethal ventricular arrhythmias when level of Cx43 drops to 18% of control levels (51). Another study reports decreased Cx43 expression and increased Cx45 expression in the failing human ventricle (52), which could potentially alter the ratio of the two connexins and cause significant effect on channel properties and overall cardiac function. Support for this comes from the increased susceptibility of transgenic mice overexpressing Cx45 to ventricular tachycardia (53). Cx40 expression is also shown to increase in failing human ventricle but this is confined to the end-stage ischemic heart disease (54).

With regard to the cellular mechanism of regulation of GJ in cardiac disease, it is shown that microRNA1 expression is increased in diseased human ventricle, and it downregulates Cx43 expression in ischaemic heart (55). Furthermore, this study also shows that blocking of microRNA1 expression by antisense prevents arrhythmia in an experimental animal model. Recently, much more attention has been given to identify interacting partners for GJ proteins which may modulate cardiac function. In this regard, it is reported that ZO-1 (zonula occludens-1) restricts the recruitment of connexons to the GJ periphery, thereby reduces the GJ size and decreased GJ in the diseased heart (56). Furthermore, plakophilin 2 (PKP2), a component of the desmosome is shown to regulate function and distribution of Cx43 (57). These authors show that decreasing PKP2 expression by siRNA in neonatal rat ventricular myocytes causes decreased Cx43 expression, significant disruption of Cx43 gap junction plaques and reduced dye coupling between cells. All these reports firmly establish the role of GJ in cardiac function; however, future studies should be aimed at understanding the regulatory mechanisms of GJ remodeling, the role of GJ in atrial fibrillation and the nature of signaling molecules that pass through GJ to modulate cardiac remodeling.

Although most studies have focused on understanding the role of GJ in heart, some studies have characterized Cx43 HC in heart cells. Functional HC in isolated adult rabbit ventricular myocytes have been detected (58;59), giving way for the possibility of HC inside this tissue. Kondo et al (2000) (59) show electrophysiologically that removal of extracellular $[Ca^{2+}]$ and metabolic inhibition allows activation of non-selective current which may have a role in alteration of ionic fluxes thereby promoting arrhythmias and myocardial infarction. During myocardial ischemia, Cx43 is dephosphorylated and activity of several protein kinases and phosphatases gets affected (60–62). The initiation of ischemia which accounts for the first few minutes does not affect the partially phosphorylated status of the physiological sarcolemmal Cx43 (63). However, prolonged ischemia corresponds with dephosphorylation of Cx43 usually associated with opened HC (60). Studies on severe pathophysiological conditions including ischemia, hypoxia and diverse forms of metabolic inhibition suggest

the role of HC in the destabilization of the ionic homeostasis and eventual cell death (58;64). During ischemia and hypoxia, the concentration of ATP is elevated in the interstitial spaces within the heart due to its release from various cell types including the cardiomyoctes. However, the mechanism for the release of ATP has been understood only recently by a study which showed a negative feedback regulation of ATP release involved HC in cardiomyocytes (65). The maxi anion channels that released the ATP suppressed the release of ATP from HC in the cardiomyocytes. In other studies signaling pathways involving mitogen-activated protein kinase (MAPK), protein kinase C (PKC) and protein tyrosine kinases (PTK) have been shown to be involved in cardiac protection during ischemia. HC phosphorylated at the MAPK signaling sites is kept closed under normal extracellular [Ca^{2+}]. However, dephosphorylation of those sites by phosphatases activated by biological stress like hyperosmolarity and metabolic stress opens the HC allowing the influx of harmful ions critical to heart physiology and pathophysiology (66).

In order to understand the contribution of HC to ischemia-reperfusion injury in rat neonatal cardiomyocytes, changes in HC activity have been investigated during *in vitro* simulated ischemia under oxygen-glucose deprivation (OGD). Transient Cx43 HC opening and increase in intracellular [Ca^{2+}] due to OGD are inhibited in the presence of a Cx43 mimetic peptide, Gap26 and lanthanum chloride as is the reduction in cell viability (67). These findings suggest that transient HC opening during OGD is responsible for cell injury. Cx43 HC is present on the sarcolemma of cardiomyocytes and remains closed under physiological conditions. However, ischemic stress opens these channels and leads to irreversible tissue damage and cell death. This study is also the first to confirm a reduction in the infarct size in the presence of Gap26, which can efficiently block HC opening thereby providing protection to intact heart against ischemia-reperfusion injury whether administered before or after the occurrence of ischemia (68). Opening of Cx43 HC appears to be an important mechanism for ischemia-reperfusion injury in the heart since Gap26 significantly reduces the infarct/risk ratio. However, pannexin-forming HC is not involved (69). Based on the studies mentioned above, it can be speculated that HC may play an important part in the ischemic preconditioning of the heart intercepted with brief periods of ischemia and timely closure of the HC. Phosphorylation by specific kinases like MAPK, PKC and CaMKII may delay the HC opening and associated deleterious consequences.

Inner ear

Several different connexins, Cx26, 30, 31, 32 and 43 are expressed in the cochlea and GJIC is observed in both the cochlea and organ of Corti (reviewed in (70)). The functional relevance of GJ in cochlear function receives much attention due to the syndromic and non-syndromic deafness caused by mutations in connexin genes. Mutations in Cx26 contribute to a large proportion of deafness caused in human population; however, other four connexins including Cx30, Cx31, Cx32 and Cx43 also have been shown to be involved in either syndromic or non-syndromic hearing loss (18;71;72). Deafness-associated connexin mutations either affect HC trafficking or produce non-functional channels or channels with defective gating and permeability properties (73). Several functions of GJ have been speculated to contribute to the normal cochlea function. In this regard, GJIC is proposed to participate in K^+ recirculation in the cochlea and in the passage of critical metabolites like IP3 (74;75). However, the exact function of GJIC in regulating cochlear physiology is yet to be investigated.

Conductance of fluorescent dye uptake assays which cannot penetrate the membrane on dissociated cochlear cells and in acute or cultured preparations of the cochlear epithelium have successfully revealed the presence of functional HCs in cochlea (76;77). These studies indicate that cochlear HC may exert a control on hearing sensitivity by releasing ATP to the exterior that could modulate the electromobility of outer hair cells. Gain-of-function

mutation resulting in abnormal HC opening at rest period has been responsible for certain deafness-related diseases (78). One deafness-linked Cx26 mutation, G45E, has been associated with a fatal form of keratitis-ichthyosis-deafness syndrome (79;80). G45E changes the charge of the amino acid side chain from neutral to negative and likely affects the Ca^{2+} binding site present on the first extracellular loop of Cx26 HC (78). Findings from Stong et al (2006) suggests that Cx26 G45E mutation causes the HC to become leaky in presence of normal [Ca^{2+}] leading to cell death (81). Cell death can however be rescued by increasing the extracellular [Ca^{2+}]. In the cochlea, Panxs 1 and 2 have been detected in the spiral ganglion and Scarpa's ganglion neurons (82). A more widespread cochlear expression of Panx1 and Panx2 has been reported and the expression of Panx3 has also been detected in the cochlear bone by a recent study (83). Molecular mechanisms of the effect of mutations impairing HC function in the ear are beginning to emerge. Development of animal model for testing the deafness-associated mutations resulting in HC dysfunction requires further investigation.

Kidney

A series of earlier studies have provided evidence for the expression of mRNAs of ten different connexins in the kidney including Cx26, Cx30, Cx30.1, Cx31, Cx32, Cx37, Cx40, Cx43, Cx45 and Cx46 (reviewed in Hanner et al (2010) (84). Cx37, Cx40, Cx43, and Cx45 are expressed in the renal vasculature (85–88) with Cx40 being predominantly expressed in the endothelial cells and Cx45 being abundantly expressed in the vascular smooth muscle cells (84). Morphological evidence for the presence of GJ plaques in the tubules exists only in the proximal tubules (89;90). Cx30, Cx30.3 and Cx37 are expressed in the distal nephron; however, it is not clear whether they form GJ or just primarily act as HC, as the presence of this connexin protein is observed only in the unopposed apical membrane of the cells. Furthermore, ultrastructural studies have shown the presence of GJ between all cells of the glomerulus (91;92) with strong Cx40 expression in the entire intraglomerular mesangium and Cx37 only in the mesanglial cells at the vascular pole of the glomerulus (87;88) and Cx43 formed GJ between the podocytes (93).

Renal connexins facilitate vascular conduction between the cells of the vascular wall (94). The propagation of vasodilation induced by acetylcholine is significantly decreased in Cx40 knockout mice (95) and by connexin mimetic peptides (96–98), suggesting participation of GJ in propagation of vasodilation. In contrast to the effect of Cx40 knockout on vasodilation, vasoconstriction induced by local application of KCl is not inhibited in the absence of Cx40 (95). The myoendothelial GJ between the endothelial cells and the vascular smooth muscle cells is suggested to mediate part of the endothelial-derived hyperpolarizing factor response, by allowing agonist-induced hyperpolarization of endothelial cell membrane to spread to the vascular smooth muscle cells (94;99).

Connexins, in particular, Cx40 have been shown to regulate renin secretion. In Cx40 knockout mice the renin producing cells disappear from the media of the afferent arteriole and appear in the glomerular tuft, the extraglomerular mesangium and the periglomerular interstitium (100). These mice are hypertensive and have increase in plasma renin concentration (101). Selective knockout of Cx45 in nestin-expressing cells results in a phenotype showing increased expression and secretion of renin, and increased blood pressure (102). Though data from Cx43KI32 mice, where Cx43 is replaced with Cx32, points to role of Cx43 in renin secretion (103), Conditional knockout of Cx43 in endothelial cells has no effect on renin secretion (104;105), suggesting that more studies are needed to clearly establish a role for Cx43 in renin secretion.

In spite of the expression of connexins in the tubules, not much is known about their physiological role in the tubules. Some studies however, indicate that the level of Cx30 and

Cx37 is modulated by dietary salt levels (106;107). Even though most kidney cells have GJ, knockout of individual connexins have only minor effect on development of kidney (108–110). Connexin mimetic peptides against Cx37, Cx40 or Cx43 increase blood pressure, which is prevented by co-treatment with losartan, the angiotensin receptor blocker (111), suggesting that connexin-mediated modulation of blood pressure is through the renin-angiotensin system. Data from Cx40 knockout mice supports these observations (112).

Activation of Cx43 HC has a role in the pathogenesis of renal ischaemic lesions. Human renal proximal tubule cells (hPT cells) express Cx43 protein in the plasma membrane. Moderate ATP depletion activates HC in hPTcell monolayers and increases cell death. HC activation may dissipate solute fluxes across the cell membrane and amplify other deleterious effects of ATP depletion. These fluxes, if not appropriately replaced, will alter intracellular concentrations causing cell damage and impairing the recovery from the metabolic insult when the ischaemia is relieved (113;114). Expression of Cx30 has been observed throughout the luminal membrane of select cells in the distal nephron with the highest level of staining observed in the distal convoluted tubule. Indeed, high salt upregulates Cx30 expression which may function as a HC involved in the regulation of salt reabsorption in the distal nephron. More detailed studies on HC in the kidney are required to understand their role and regulatory mechanism.

Lens

Lens expresses three different connexins including Cx43, 46 and Cx50. The lens with an anterior epithelium and posterior fibers continues to grow in volume throughout the life of an organism, differentiating new fiber cells from the equator region. The older fiber cells do not turnover and remain in the interior of the lens. The lens differentiating fiber cells synthesize high amounts of the soluble protein crystallin to achieve transparency and high refractive index, and then lose their nuclei and the light scattering organelles. Thus the lens fiber cells are dependent on the anterior epithelial cells for their metabolic needs. The lens fiber cells communicate with each other and the epithelial cells through large number of GJ (115). The lens epithelium has abundant expression of Cx43 and Cx50 (116;117), and Cx46 and Cx50 form the GJ between the lens fiber cells (118;119). Mutations in Cx46 and Cx50 have been linked to development of lens congenital cataracts in humans and rodents (reviewed in Jiang (2010) (22)). Some of these are loss-of-function mutations, whereas others are dominant negative in nature.

Even though Cx46 and Cx50 colocalize in all junctional plaques in the fiber cells, targeted deletion of these connexins results in unique cataracts with distinct difference in the timing of onset and morphology (120;121). Cx46 knockout mice develop nuclear cataracts and the opacity of the lens is possibly due to accumulation of cleavage products of γ-crystallin (120). Furthermore, loss of Cx46 causes accumulation of calcium and subsequent activation of Lp82, a calcium-dependent protease (122). The deletion of Cx50, but not that of Cx46, results in delayed postnatal growth, decreased lens size and micropthalmia (121). Stimulation of epithelial proliferation and fiber cell differentiation has been proposed as the underlying mechanism of Cx50-mediated lens growth (123;124). Our group reports that chick Cx50, but not Cx46 and Cx43 stimulates epithelial to fiber cell differentiation and this stimulatory effect appears to be independent of epithelial cell proliferation (123). Furthermore, our group shows that the C-terminus of Cx50 is required for Cx50-mediated lens cell differentiation (125). Another report suggests that in Cx50 knockout mice epithelial cell proliferation is compromised (124). Lenses without Cx50 lose their sensitivity to pH in response to acidification in the differentiating lens fiber region (126). Replacing the coding region of Cx50 with that of Cx46 restores lens transparency but fails to rescue the normal growth (124;127).

Cx43 knockout neonatal mice lenses have loose apposition of epithelial cells and fiber cells with dilated extracellular spaces and intracellular vacuoles (128). In contrast to this finding, another study shows that Cx43 knockout lenses have normal development through embryonic day 19 (129). The Cx43 and Cx50-double knockout mice lenses are structurally normal; however, there is great reduction of GJ between the epithelial cells and the epithelial-fiber cells with no change in degree of communication between fiber cells (129).

Although an extensive network of GJ spanning the vertebrate lens is essential for transparency and homeostasis, several reports point to other roles of Cx50 which are not related to GJ function. Overexpression of chick Cx50 promotes lens epithelial-fiber differentiation, but fails to increase intercellular coupling (123). GJ-deficient mutants stimulate lens epithelial-fiber differentiation to similar level as wild-type Cx50 (125). Several studies demonstrate the roles of Cx46 and Cx50 HC in lens development. Cx46-forming HC is gated by calcium and voltage, and is also mechanosensitive (130;131). Due to their mechanosensitive nature, Cx46 HC is proposed to possibly assist in accommodation of the lens by providing transit path for volume flow as the lens changes shape (130). HC formed by Cx50 is sensitive to cations like Na^+ and K^+ (132). The density of Cx50 HC is also directly proportional to the magnitude of the Cx50 Ca^{2+}-sensitive current. Structural studies indicate that there are far more Cx50-forming GJ channels compared to Cx50-HC in the lens (133). A study from our laboratory has shown that PKA activation enhances both Cx50 GJ and HC functions (134). Cx50 in the chick lens is phosphorylated *in vivo* by PKA at residue Ser-395, which is a highly conserved amino acid residue across different animal species.

Liver

This is one of the first organs where gap junction channels were detected. In isolated liver, plasma membranes, Revel and Karnovsky in 1967 showed the presence of hexagonal arrays of subunits in the intercellular junctions (135). In 1974, Goodenough characterized the gap junction proteins from mouse hepatocytes and named them as connexins (136). Gap junctions are abundant in hepatocytes and mostly are composed of Cx32 and Cx26 (137;138). Cx37 and Cx40 are mostly expressed in the liver vascular cells (139), whereas Cx43 is expressed in the nonparenchymal liver cells (140). Apart from a few conflicting reports, most studies show that in the hepatocyte life cycle, GJIC increases during the G1 phase but decreases dramatically upon initiation of the S phase (141–146). Similar pattern is observed for the expression of Cx32 and to a great extent for Cx26, however, Cx43 expression remains unchanged (141;144;146). Though an alteration in GJIC and connexin expression is observed during hepatocyte cell cycle, the relevance of such changes is not clearly understood. In the Cx32 knockout mice, the proliferative activity of the hepatocytes of regenerating rat liver is not increased, however, the extent of synchronous initiation and DNA synthesis termination is decreased, suggesting decrease GJIC likely permits cell cycle progression but does not provide any direct signal for cell division (146) (147). In contrast to this others believe that gap junctions play a very critical role in regulating cell proliferation rather than just assisting in cell cycle progression. In line with this, overexpression of Cx32 and Cx26 in liver epithelial cells and hepatoma cells increases expression of p27 and E-cadherin respectively leading to decrease cell proliferation (148;149). Apart from changes in connexin expression during proliferation, several groups have shown changes in expression of these gap junction proteins during differentiation of early rat hepatic progenitor cells into adult liver parenchymal cells (150;151). GJIC regulates several liver specific processes including albumin secretion, ammonia detoxification (152), glycogenolysis (153), bile secretion (154) and xenobiotic phase I transformation (155–158). Since gap junctions play critical role in regulating hepatocyte homeostasis, these structures are often affected during liver toxicity. Xenobiotics induced hepatotoxicity is associated with decreased connexin

expression (159;160). Furthermore, Cx32 dominant-negative mutant transgenic rats are more resistant to chemically induced hepatic injury (161). In PLC/PRF/5 hepatoma cells, overexpression of Cx26 accelerates apoptosis (162), whereas in Hep3B hepatoma cells and WB-F344 liver epithelial cells Cx43 GJIC decreases during acute choline deficiency apoptosis (163). Wilson et al reported that GJIC increases during early phases of apoptosis whereas declines during late stages in serum deprived rat WB-F344 liver epithelial cells (164). This increase of GJIC during the initial stages of apoptosis could be to spread the cell death signal from cell to cell.

Cx32 HC have been shown to contribute to the apoptotic to necrotic transition during Fas mediated hepatocyte cell death. Fas ligands (FasL) binds to its receptors at the cell surface and triggers apoptosis in the liver (165;166). In this study, siRNA and mimetic peptides were used to inhibit Cx32 expression and the authors show that Cx32 increases the transformation of apoptotic cells to necrotic state, partially due to the ability of Cx32 to form functional HC (167). In another recent study by Vinken et al (168), Cx43 mediated signaling was shown to be responsible for induction of spontaneous apoptosis in primary hepatocytes. Cx43 expression, localization, gap junction and HC activity were monitored in freshly isolated adult rat hepatocytes. Inhibitors to Cx43 resulted in downregulation of both HC and GJ activity which paralleled with decreased expression and activity of caspase 3 as well as reduced expression of Bid.

Lungs

Gap junctions play critical roles in the lung. GJIC in the airways regulate calcium signaling between ciliated epithelial cells which thus regulates ciliary beating (169). Gap junctions also play a role in regulating secretion of pulmonary surfractants by type II alveolar epithelial cells, in passing calcium transients from the type I alveolar cells to the type II cells (170) and in propagating intercellular signals from one alveolus to the other (171). The endothelial cells in the normal lung predominantly express Cx37, Cx40 and Cx43 (172–174). Cx26, Cx32, Cx43 and Cx46 are the major connexins expressed by alveolar epithelial cells and Cx30.3 and Cx40 are expressed at a very low level (175).

Cx43 in the pulmonary endothelium is required for propagation of calcium waves along pulmonary vessels as these waves are absent in the Cx43-deficient mouse model (176). These calcium waves induced by mechanical stimulation are shown to increase pulmonary endothelial P-selection expression at the cell surface, suggesting a role of Cx43 in spreading proinflammatory signals. This effect of Cx43 is counterbalanced by Cx37, which is found in circulating monocytes, macrophages and macrophage foam cells in early and late atherosclerotic plaques (177). Cx37 HC can release ATP into the extracellular space (178) and thereby prevent leukocyte adhesion in primary monocytes and macrophages and inhibit inflammation (179). In addition, a recent study indicated to the role of pannexin 1 for the release of ATP in the airway epithelial cells (180).

Connexins in the lung also contribute to improved barrier function. Though lung barrier function is mainly regulated by tight junctions, gap junctions are often seen adjacent to tight junction strands (181). Role of gap junctions in improving barrier function comes from studies where inhibition of GJIC by glycyrrhetinic acid or oleamide decreases barrier function by 50 to 75% (182) and expression of Cx32 increases barrier function of immortalized hepatocytes from Cx32-deficient mice by ~25% (183). In addition to the role of GJIC in improving barrier function, this form of intercellular communication also plays important role in preventing lung injury. Mice lacking Cx40 and endothelial Cx43 develop symptoms similar to pulmonary fibrosis spontaneously (184). However, Cx40 alone or endothelial Cx43 alone deficient mice did not show any obvious pulmonary phenotype. However, these mice showed decrease lung barrier function, disorganized alveoli and

extracellular matrix deposition after 8 weeks of birth (104;185;186). Although different connexins are expressed in the lung, Cx43 seems to play important role in alveolar function. Interestingly, newborn Cx43 knockout mice are cyanotic (32), however, this could have been caused due to defect in cardiac outflow. In this regard, lung targeted Cx43 knockout would provide valuable insight into the role of Cx43 in overall functioning of lung.

Mammary Gland

The expression and function of connexins are dynamically regulated throughout mammary gland development and differentiation. In normal human mammary epithelial cells, expression of Cx26 and Cx43 messengers and proteins is observed by Northern blot and immunocytochemistry, respectively, and functional GJIC is revealed by dye transfer experiments (187). Normal human mammary fibroblasts are also shown to express Cx43 and heterocellular GJIC is observed between the fibroblasts and epithelial cells (188). Cx43 was shown to be mostly present in the myoepithelial cells (189–191), with sparse expression in some luminal cells of the mammary gland *in situ* (192) and Cx26 expression is found predominantly between the luminal cells of ducts (190). From these expression patterns, it seems likely that Cx43 is required for myoepithelial differentiation, whereas Cx26 has more variable role in luminal cell function. Cx26 protein levels reach highest expression at the onset of lactation and decreases during involution (193;194). Cx26 is shown to be present between luminal cells of the ducts at the basolateral borders and in all stages of development (189;194). Though this expression profile of Cx26 suggests its role in milk production and secretion, its expression in virgin mouse mammary glands and nonpregnant human breast tissue suggests that this connexin possibly also has a role in the differentiation and homeostasis of this gland. Conditional suppression of Cx26 in the mammary epithelium before puberty leads to the impairment of development of lobular structure of the gland and lactation; however, conditional knockout during pregnancy has no developmental outcome (195).

Apart from Cx43 and Cx26, mouse mammary gland also expresses Cx32 and Cx30. Cx30 mRNA expression is identified in pregnant and lactating mouse mammary gland (194;196) and the protein expression is first detected at postnatal day 15 and followed a peak onset at lactation and decline in involution similar to Cx26 (194). Cx32 mRNA is first detected at parturition and lactation (189;197). Though studies from several groups report its expression at the basolateral regions of the luminal cells in the lactating gland (189;193;197), Talhouk et al (2005) (194) show the expression of this protein throughout all developmental stages. In the Cx32-null mice, the mammary glands develop and function normally suggesting that this connexin is dispensable for the development of the mammary gland (195). Cx26 and Cx32 co-oligomerize in the luminal epithelial cells of the mouse mammary gland and at the onset of parturition Cx32 is only found in heteromeric channels having Cx26 and during lactation the ratio of Cx32 increases to form the homomeric Cx32 connexons, probably to allow the passage of larger molecules including cAMP and cGMP (198).

In contrast to the expression pattern of Cx26 and Cx30, Northern and quantitative PCR analysis reveal that Cx43 transcript decreases during mid-pregnancy, disappears during lactation and reappears during involution (194;199). During last days of pregnancy and at the onset of lactation, a shift to the more highly phosphorylated species of Cx43 is evident without any change in the total Cx43 protein level (194). Cx43 is shown to be expressed at the cell surfaces between the basal myoepithelial cells (189) and at the myoepithelial-epithelial junction (194). Cx43 knockout mice die at birth (32) and conditional mammary gland-specific Cx43 knockout mice is not available. However, heterozygous knockin mice in which Cx43 gene is replaced by Cx32 show defects in milk ejection, though they have normal mammary gland development and milk production (200). Inhibition of GJIC in mammary epithelial cells *in vitro* inhibits secretion of the milk protein -casein (201). These

studies implicate role of connexins and GJIC in mammary gland development, milk secretion and ejection.

Nervous System

The central nervous system (CNS) has 11 different connexins and is highly coupled through GJ network (202;203). Cx26, 30, 32, 36, 37, 40, 43 and 45 are well expressed in the brain with a unique expression pattern for each one during differentiation (204). Intercellular coupling occurs between neurons, astrocytes, oligodendrocytes, microglia, ependymal cells and also between astrocytes-oligodendrocytes or neurons-astrocytes (reviewed in Talhouk et al (2008)(205)). Connexin function is well established in neurogenesis, cell migration, neuronal development, differentiation and morphogenesis (206;207). Inhibition of GJ function in postnatal day 19 mouse embryonic carcinoma cells in a model of neuronal and glial differentiation prevents the appearance of astrocytic and neuronal phenotype (208), suggesting role of GJIC in glial cell function. Role of GJ in neuronal migration is elucidated by the delayed neocortical neuronal migration in the Cx43-null mutant mice (207). Knockdown of Cx26 and Cx43 in embryonic day-16 cortex by shRNA prevents migration of neurons along radial glia in the intermediate zone and loss of cells that arrive in the lower and upper cortical plates (209). Interestingly, these migration defects are rescued by a channel-dead mutant whereas mutants with loss of connexon pairing (not HC activity) and C-terminal truncations fail to rescue the defects, suggesting that channel-independent function of connexins contributed to proper neuronal migration. Mutations in Cx32 underlie the X-linked Charcot-Marie-Tooth syndrome leading to failure of myelination of the Schwann cells (210).

GJIC plays a critical role in determining susceptibility of brain to hypoxia-ischemia injury. In an *in vitro* model of ischemia, inhibition of GJ function by carbenoxolone and by Cx26 and 32 knockdown significantly reduces cell death (211). Similar neuroprotection is also observed upon inhibition of GJ function by chemical inhibitors or in organotypic slices from Cx43 knockout mice in a traumatic brain injury model (212). Further evidence for role of GJIC in neuronal ischemic injury comes from studies, where administration of carbenoxolone to ischemic pups after intrauterine hypoxia-ischemia decreases neuronal damage (213). Several *in vivo* studies also confirm contribution of GJ to ischemia. Pretreatment of rats with octanol, the gap junction blocker during ischemia induced by occlusion of the middle cerebral artery reduces the infarct volume (214). Administration of octanol in a transient forebrain ischemia model decreases neuronal cell death (215). All these experimental evidences clearly point to the role of GJ in contributing to the cell death after hypoxia and ischemia; however, GJ themselves undergo significant changes following ischemia. Thus future studies should be directed towards the underlying mechanism of GJ modulation of cell death during ischemia including the nonchannel- dependent function of connexins in regulating susceptibility of cells to hypoxia-ischemia.

Both connexin and pannexin HC form an integrated network of channels present in the astrocytes and neurons. The majority of the cell types in the CNS have the potential to express HC activity but the physiological relevance of HC has just begun to be uncovered. One of the major GJ forming proteins of astrocytes is the Cx43. Cx43 HC in astrocytes and C6 glioma cells may mediate the release of gliotransmitters like glutamate and ATP. Interestingly, several reports demonstrate that Cx43 expression and zero extracellular [Ca^{2+}] potentiate ATP release from C6 gliomas which is inhibited by GJ/HC blockers (14;216;217). However, the role of Cx43 HC in ATP release is not a widely accepted concept. It has also been suggested that ATP release from astrocytes is mediated by the purinergic receptor, P2X7 and not by the Cx43 HC since ATP release was absent in P2X7−/− spinal cord astrocytes but not those from Cx43−/− mice (218). Several other connexin-forming HC have been observed in the different cells of the nervous system with associated pathological

implications. GABAnergic interneurons in the neocortex and hippocampus as well as neurons in the olivary nucleus and cerebellum express Cx36 (219;220). Although, formation of Cx36 GJ is known, formation of Cx36 HC is as yet questionable. There are contrasting views about the presence of HC formed by Cx36. One study suggests that Cx36 does not form HC because oocytes injected with Cx36 mRNA showed no HC activity even in the absence of extracellular [Ca^{2+}] (221). However, another study reported Cx36 HC opening in cortical neurons in the presence of very high K^+ (100 mM) or KCN with the release of ATP and induction of ischemic tolerance (222). Moreover, Cx36 siRNA-treated neurons show reduction in cell death induced by combined KCl/KCN. Cx45 is also expressed in axons. Although biophysical properties of Cx45 are extensively characterized, functional role as a GJ and HC is not quite clear. Under normal conditions of negative membrane potential and external 2 mM [Ca^{2+}], the open probability of the Cx45 HC is low suggesting a strong influence of membrane potential on the HC activity (223).

Cx30 is also expressed in astrocytes (224) and cochlea (225). It forms GJ and mutations in Cx30 cause deafness (226). However, to this date there is no strong evidence to support the role of Cx30 HC in astrocytes but two mutations in Cx30 (A88V and G11R) form functional HC at the cell surface but generate a leakage of ATP when expressed in HeLa cells (227). Currently, evidence for connexin-based HC in neurons and astrocytes is weak and needs further validation in the *in vivo* system to support studies done in cultured cells. Several reports have provided center stage to the possible role of pannexins as HC in the brain. Among the three known isoforms of pannexins, Panx1 and Panx2 are expressed in the brain in the hippocampus, neocortex, cerebellum, thalamus and hypothalamus whereas the Panx3 appears solely in skin and osteoblasts (228–230). Panx1 expression has been reported in cultured astrocytes, oligodendrocytes and neurons (231), but is absent in C6 glioma cells (26). Neurons show increased expression of Panx2 but astrocytes express Panx2 only upon ischemia/reperfusion (232). In a recent study (233), FGF1 released during spinal cord injury induces activation of spinal actrocytes in culture to release ATP during early time period of 2 hours by Panx1 HC activated by P2X7 receptor, and 7 hours later, both Cx43 HC and Panx1 HC are involved in the ATP release. Interesting speculations also indicate that signaling molecules released from one cell type (neuron) may affect the HC on a nearby cell type (other neurons or astrocytes). Appreciably, the current status of the connexin and pannexin HC in the CNS clearly suggest of cooperative gating mechanisms or features of the conduction pathway that differentially regulate the ionic and metabolic fluxes.

Skeletal Tissues

GJ regulates development, differentiation and remodeling of the bone. Though three different connexins including Cx43, Cx45 and Cx46 are expressed in the bone cells, Cx43 is the most abundant isoform. Direct evidence for a role of Cx43 in skeletal development comes from the malformation of limbs and truncation of limb buds in chick embryo after incubation with Cx43 antisense oligonucleotide (234). Similar observation is reported in dissociated embryonic chick mandibular mesenchyme treated with Cx43 antisense, which is further confirmed by the delayed ossification of the cranial vault, vertebrae, clavicle, ribs and limbs in Cx43-null embryos (235). The osteoblasts isolated from these mice also have decreased mineralization potential as compared to wild-type control cells. ODDD in human patients due to Cx43 mutations causes craniofacial abnormalities, syndactyly of the hands and foot and hypoplasia (23;236;237). Mutagenesis screening in mice identifies a G60S substitution in Cx43 which results in bone defects similar to that of human ODDD (238). The role of Cx43 in adult skeleton has been studied using conditional knockout of Cx43 in osteoprogenitors, osteoblasts or osteocytes. Osteoblast-specific deletion of Cx43 in mice causes low bone mass, reduced bone formation and attenuated anabolic response to PTH treatment (239). Deletion of Cx43 using Dermo1 (Twist2)-Cre system, which drives

expression of Cre in mesenchymal condensations, the cells that give rise to osteoblast and chondrocyte lineages, develops age-related osteopenia (240). In contrast to these findings, knockout of Cx43 using Cre recombinase driven by osteocalcin promoter, which drives Cre expression in the mature osteoblasts, does not have any effect on overall bone mass (241). However, bone mineral density (BMD) of these mice is measured between 2 and 4.5 months of age, thus, effect of Cx43 knockout on bone density after peak bone mass accrual cannot be ruled out. Further evidence for regulation of bone development by Cx43 comes from transgenic mice overexpressing microRNA 206 (miR206) (242). These mice have a low bone phenotype. Cx43 is found to be a target of this microRNA and overexpression of Cx43 in the miR206 expressing osteoblasts restore their differentiation potential. In 3D cultures overexpression of Cx43 in bone marrow stromal cells is shown to enhance osteogenic differentiation (243). GJIC is shown to regulate chondrocyte differentiation as inhibition of GJ function decreases production of proteoglycans and type II collagen (244). Similar to chondrocytes, GJIC is also shown to positively regulate osteoblast differentiation (245). Apart from the role of connexins in overall bone development, GJ and HC have also been suggested to regulate mechanotransduction in the musculoskeletal system (246;247). Fluid flow and mechanical stimulation are shown to increase GJIC and open Cx43 channels leading to the release of important bone anabolic molecules (4). HC has been demonstrated to exist both in osteoblasts and osteocytes (248–250). Clearly, HC in osteocytes appears to have essential, distinctive roles in transmitting the signals elicited by mechanical stimulation to other bone cells and the extracellular matrix, and further promote bone formation and remodeling (246). Some years ago, we found that in addition to GJ, Cx43 forming HC also mediates the biological responses like PGE_2 release elicited by fluid flow (16). Fluid flow-mediated release of PGE_2 increases the surface expression of Cx43 to open HC.

Besides the release of bone modulators like PGE_2, Cx43 HC may allow the transfer of other key molecules to and from osteocytes; however, the identity of these factors remains to be defined. Bisphosphonates have also been shown to open the Cx43 HC present on the osteocytic cells by triggering the activation of Src and ERK kinases for promoting cell survival (249). Study by Genetos et al (2007) (251) demonstrates that fluid flow activates HC in MLO-Y4 osteocytic cells through a mechanism involving PKC, which induces ATP and PGE_2 release. To understand how Cx43 HC are responsive to mechanical stimulation, we study the mRNA expression of the proteins upregulated upon mechanical stimulation and affected by blocking activity of Cx43 HC using the antibody against the extracellular loop of Cx43 (252). We recently show that integrin $\alpha5\beta1$ associates with Cx43 forming HC in bone osteocytic cells and facilitate channel opening upon shear stress (253). Integrins are known mechanosensors on cell surface as mechanical stimulation applied on bone can be directly sensed by integrin molecules and transmit the signals across cell membrane (254–256). Although, osteocytes are the known mechanosensory cells in the bone but which part of the osteocytes is the real sensor of mechanical stimulation which opens the Cx43 HC has been a mystery. Our recent study shows that Cx43 HC opening is only observed in the cell body part of the osteocytes and not the dendrites suggesting the presence of HC on the cell body (257).

HC formed by pannexins has also been reported in bone osteoblasts and osteocytes (258). Panx3 expression has been demonstrated in osteoblasts (83). In a very recent finding, Panx3 promotes osteoblast differentiation by functioning as an ER Ca^{2+} channel and a HC, and by forming GJ (259). HC formed from Panx3 releases ATP and activates the purinergic receptors which further activates PI3K/AKT signaling and promotes osteoblast differentiation. Clearly, HC formed in the bone has the ability to control the survival and death of the different bone cells and thereby regulate the bone remodeling process apart from the GJ.

Testis

Expression of 11 different connexin isoforms, including Cx26, Cx31, Cx31.1, Cx32, Cx33, Cx37, Cx40, Cx43, Cx45, Cx46 and Cx50, has been reported in the testis among which Cx43 is the predominant connexin (260). Direct evidence for a role of Cx43 in testis comes from a 50% depletion of primordial germ cells (GCs) in fetal male mice with Cx43 knockout (261) and the decreased number of GCs is demonstrated to be a result of increased apoptosis of these Cx43 knockout cells (262). This same observation is also confirmed by an *in vitro* study, which shows that Cx43 GJ function regulates GC number by affecting survival of spermatogonia (263). The decrease in Cx43 expression in the knockout mice not only affects the number of GCs, but also the expression patterns of other testicular connexins. The knockout mice have detectable mRNA expression of four different connexins as opposed to wild-type expressing eight members of connexin family (261). The role of Cx43 in spermatogenesis is also confirmed by knockin studies in which Cx43 gene is substituted by either Cx26 (264), Cx32 or Cx40 (200) coding sequences. These mice also show defective spermatogonial amplification further emphasizing critical role played by Cx43 channels in regulating testis function. The sertoli cell-specific Cx43 conditional knockout mice have reduced testis size, weight, an arrest of spermatogenesis at the level of spermatogonia or sertoli cell-only syndrome. Furthermore, these mice show reduced number of spermatogonia and increased number of sertoli cells per seminiferous tubules (265;266). These knockout mice and *in vitro* studies provide evidence for negative regulation of sertoli cell proliferation by Cx43 (263;267). Taken together these studies point to critical role played by connexin 43 and GJIC in regulating testicular function. However, the exact mechanism by which GJ or HC regulates the development of GC is still unknown. Until now, not much is known about the possibility of HC in the testis.

Ovary

The ovarian follicles of rodents express Cx32, Cx37, Cx43 and Cx45 (Reviewed in Kidder and Mhawi, 2002 (268)). Since Cx43 and Cx37 are the most predominant connexins in the ovary of many species, their role in ovarian function has been studied the most. GJIC is reported to regulate folliculogenesis, meiotic arrest and apoptosis of female gonad. Communication between oocytes and the somatic cells is established from primordial stage of follicle development and continues throughout the follicular development period (269), GJ has been suggested to transfer amino acids and nucleotides from the somatic cells to the oocyte (270;271). In the Cx37 knockout mice folliculogenesis is arrested at the early antral stage, the oocytes do not reach their full size and also fail to have full meiotic potential (272;273). Since Cx43 knockout mice die soon after birth, ovaries from prenatal mice are grown either *in vitro* in organ culture or *in vivo* under the kidney capsule of wild type mice. Under both *in vitro* and *in vivo* condition, folliculogenesis is arrested at the primary follicle stage and oocyte growth is retarded (261;274). These oocytes fail to undergo meiotic maturation and fertilization. GJ has been shown to play a role in the transfer of cAMP, which maintains the fully grown oocytes in a meiotically arrested state, from the somatic cells to the oocyte (275). Decreased ovarian Cx43 expression in acute hyperglycemia and chronic diabetes results in increased number of apoptotic follicles (276). In consistence with this, ovaries of Cx43 knockout females have reduced number oocytes (261) due to increased primordial germ cell apoptosis (262). Decreased expression of Cx43 in apoptotic follicle is also observed in bovine and porcine ovary (276;277). In contrast to decreased expression of Cx43 in the apoptotic follicles, Cx32 expression is increased in the bovine apoptotic follicles (277).

Cx43 is strongly expressed in the granulosa cells of the ovary where it forms both GJ and HC. It is also required for the ovarian follicle development in the mouse. Indeed, a study shows that application of mechanical stimulation or reduction of extracellular divalent

cations in the granulosa cells trigger Cx43 HC opening (278). ATP release is also detected, and can be abolished by connexin-channel blockers. Cx43-deficient granulosa cells do not exhibit any of the HC-mediated activities suggesting that HC account for the essential role of Cx43 in folliculogenesis.

2. Connexins, gap junctions and hemichannels in stem cell development

Stem cells communicate with each other to determine cell fate. Three different connexins including Cx31, Cx43 and Cx45 proteins are expressed in the undifferentiated mouse embryonic stem cells (mESCs) (279) and these mESCs have been shown to have functional GJIC. Knockdown of Cx43 in these cells reduces their proliferation without affecting their survival (279;280), upregulates expression of differentiation markers, downregulates stem cell marker levels (280). These knockdown cells also fail to form embroid bodies, suggesting that GJIC is required to maintain these cells in an undifferentiated stage and initiate differentiation. Though several previous reports show expression of only Cx45 and Cx43 mRNA in human hESC (281–283); however, another study shows mRNA expression of almost all connexins, except Cx40.1 and Cx50 (284). Dye coupling and ionic coupling reveal functional GJIC between these hESC (284;285). The pluripotent factors Oct4, Sox2 and Nanog are shown to transcriptionally regulate Cx43 expression (286), suggesting possible role of Cx43 in regulating pluripotency of hESC. Inhibition of GJ function results in increased apoptosis and reduced colony growth of hESC grown in low serum; however, the GJ blocker has no effect on hESC grown in fetal calf serum (287). Mesenchymal stem cells (MSCs) that readily differentiate into adipose tissue, tendon, cartilage and bone (288) also express connexins including Cx40, Cx43 and Cx45 (289) and coupling of these MSCs with umbilical vein endothelial cells have been reported to promote the former's osteogenic differentiation (290). Future studies should be directed towards identification of molecules that passes through GJ channels and modulate stem cell commitment and differentiation.

Cell-extracellular matrix (ECM) interactions and GJIC together influence developmental specification of neural stem and progenitor cells (NPCs). GJIC increases in the CNS after hypoxia and ischemia (205). It is an important link between grafted neural stem cells (NSCs) and host cells after NSC engraftment (291;292). Recently, a study shows that murine NSCs (C17.2) subjected to hypoxic preconditioning before the engraftment increase Cx43 expression and improve subsequent graft and host communication (293). Exposure to hypoxia increases the number of Cx43 aggregates in treated NSCs, which corresponds with enhanced HC function. Enhanced HC activity is demonstrated by faster calcein dye efflux and an augmentation of the early functional graft and host communication. In a previous study, progenitor to a teratocarcinoma progenitor line NT2/D1 that can be induced to differentiate terminally into functional hNT neurons and NT-G nonneuronal cells forms functional GJ as well as open HC in nonjunctional membranes. GJ and HC activity are assessed by the GJ blocker 18α-glycyrrhetinic acid (GA) and the dual-specificity chloride channel/connexin HC inhibitor flufenamic acid, respectively. A change in pattern of connexin expression in NT2/D1 cells undergoing differentiation is observed with a substantial reduction in dye coupling and dye uptake (294). HC in stem cells development is a much recent subject of research; however, current interesting insights would surely facilitate further identification and understanding of HC in this field.

3. Connexin, Gap junctions and Hemichannels in Cell Growth and Cell Cycle Control

Mitotic cells in mouse and *Xenopus* laevis embryos display reduced GJIC (295;296). Role of connexins in cell cycle regulation has been mostly derived from studies in regenerating liver and these studies describe a transient increase in GJIC in G1 phase followed by a

dramatic decrease in the S phase (143;297). In other systems connexins are indispensable for cellular proliferation (124;298). Genetic depletion of Cx26 and 32 only slightly increases the basal proliferation rate of hepatocytes and in the regenerating liver of Cx32 knockout mice hepatocytes do not proliferate faster (146). Chemical inhibition of GJIC has been shown to both promote and inhibit cell cycle progression (reviewed in (299)). Inhibition of cell cycle progression has been shown to be accompanied by decreased expression of cyclin D1 and D2, cdk2,4 and 6 (300). Though GJIC has been shown to regulate cell cycle progression; the underlying mechanism is yet to be identified. In this regard, recently, increase transport of calcium *via* GJ is shown to cause the G0/G1 cell cycle arrest in human hepatoma cells (301). Furthermore passage of cAMP and guanosine-3',5'-cyclic monophosphate through GJs are shown to maintain meiotic arrest in mouse oocytes (302;303). Thus connexins are speculated to regulate cell cycle either by direct exchange of growth regulatory molecules between adjacent cells or through paracrine regulation *via* HC and/or through direct or indirect interaction with cell cycle regulatory proteins.

Connexin HCs are important players in the maintenance of cellular homeostasis. A recent study shows that proliferation of activated $CD4^+$ T cells can be controlled by Cx43 HC (304). Murine T lymphocytes are known to upregulate Cx43 expression upon activation and in this study activated $CD4^+$ T cells shows elevated S368 phosphorylation compared to resting T cells. However, proliferation of activated $CD4^+$ cells is reduced in the presence of a connexin mimetic peptide Gap27, known to block GJIC by targeting its extracellular loop (305). In yet another interesting study, Cx43 expression is upregulated at chronic wound margins suggesting that downregulation of Cx43 is important for wound healing (306). Inhibition of Cx43 communication by Gap27 promoted skin cell migration of keratinocytes and fibroblasts. To understand the molecular mechanism of the action of Gap27 on wound healing in skin tissue, and diabetic and non-diabetic cell cultures, the same group shows that Gap27 decreases dye spread, accelerates wound healing and elevates cell proliferation in skin. In non-diabetic cell cultures Gap27 decreases dye uptake through connexin HC and shows enhanced migration and proliferation (307). Cells of diabetic origin are less susceptible to Gap27 during early passages, but shows comparable effects to non-diabetic cells in late passages. The cause of the discrepancy between diabetic and non-diabetic cells correlates with decreased connexin HC activity in diabetic cells but excludes differences in Cx43 expression, localization and Ser368-phosphorylation (307). HC has also been proposed to influence the growth of central nervous system. During the brain development, connexins are temporally and spatially regulated suggesting they play an important role in the proper formation of the central nervous system. Cx32 and 43 are overexpressed in a pheochromocytoma cell line derived from the rat adrenal medulla which is called the PC12. Overexpressed connexins enhance neurite outgrowth in PC12 cells treated with nerve growth factor to initiate neuritogenesis which are due to functional HC formation as opposed to GJ (308). Additional analysis reveals that ATP is released into the media likely through HC and acts on purinergic receptors to cause enhanced neurite outgrowth. NAD^+ released from HCs has been shown to influence proliferative activity as well. Released NAD^+ is processed by an integral membrane protein, the ectoenzyme cluster of differentiation 38 (CD38) which possesses an active extracellular site where it converts NAD^+ to yield cyclic ADP-ribose (cADPr). cADPr reenters the cell or moves to another cell and acts as a second messenger by inducing calcium release from the endoplasmic reticulum (309). Work from Franco and co-workers demonstrates a role for Cx43 HC in the stimulation of cell proliferation *via* reduced S phase in mouse fibroblasts cultures resulting from an increase in calcium concentration (310). Increase in calcium is an effect of the cADPr which is a calcium mobilizer. Cx43 HC releases NAD^+ which is converted to cADPr. In addition, HC could possibly be an important requirement for the normal interkinetic nuclear movement of the retinal progenitor cells. Normal interkinetic movement is a characteristic of progenitor cell nuclei during the G1 and G2 phase of the cell cycle in order to maintain repeated

divisions necessary for expansion of the progenitor pool. There are factors which affect the speed of the movement thereby altering the duration of the cell cycle. Targeting the HC activity by a mimetic peptide Gap26 slows the normal interkinetic movement the duration of the cell cycle (311).

Several lines of evidence suggest a role for the pannexin HC in cell proliferation. Activation of T cells upon binding to the antigen presenting cells (APC) results in the release of ATP from the Panx1 HC in a calcium-dependent manner (312). Released ATP binds to the purinergic receptors on the APC and activates MAPK signaling which stimulates T cell activation in an autocrine manner. Recently, Iwamoto and colleagues show that Panx3 HC can regulate the intracellular ATP/cAMP levels to promote chondrocyte differentiation (313). Chondrogenic cells transfected with Panx3 cDNA show reduction in parathyroid hormone (PTH) induced cell proliferation by release of ATP to the external environment and thereby lowering of ATP levels inside the cell and further a decrease of cAMP/PKA/cAMP signaling cascade and affecting cell growth and suppressing proliferation to initiate differentiation.

4. Connexins and carcinogenesis

Decrease of connexin expression has been linked to increased susceptibility to cellular transformation and carcinogenesis based on data demonstrating decreased connexin expression in a wide variety of cancer cell lines and tumors (314–316). Furthermore, transfection of several cancer cells including hepatoma, breast carcinoma, cervical adenocarcinoma, HeLa, glioblastoma with connexin cDNAs inhibits their growth (317–319). Connexin-mediated cancer growth suppression is initially proposed to be mediated by exchange of some growth inhibitory signals; however, recent studies also provide evidence for GJ-independent role of connexins in regulating tumorigenesis (320;321). In this regard, Cx43 overexpression in human breast tumor cells, E9 mouse lung carcinoma and osteosarcoma cells results in decreased cyclin D1 expression (322;323). In osteosarcoma cells, Cx43 overexpression results in downregulation of cyclin D1, S phase kinase-associated protein 2 (skp2) and upregulation of p27kip (324). This decreased expression of skp2 by Cx43 overexpression is not prevented by GJIC inhibitors, suggesting GJ-independent regulation of cell cycle by Cx43 (323). Similar observation is reported in HEK293 cells, where phosphorylation of Cx43 on S262 by protein kinase C prevents growth suppressive effect of this connexin, independent of the GJ forming ability (325). These findings point to GJ-dependent and -independent regulation of tumorigenesis by connexins.

In contrast to the decreased connexin expression and subsequent cellular transformation, several studies have reported high levels of connexin expression and increased GJIC in invasive tumor cells. Cx26 and Cx37 are expressed on the plasma membrane of cells invading the lymph nodes, even though their expression is reduced in the early stages of tumorigenesis (326). Similar findings are reported in prostate (327;328), breast (329) and glioma (330) cancer cells. Furthermore, overexpression of Cx43 in HeLa cells increases their metastatic potential (331). In melanoma cells Cx26 level is unchanged in the basal layer; however, when these cells invade the dermis the expression of this connexin is upregulated and GJ is formed between the cancer cells and the endothelium (332;333). Though all these models suggest a positive correlation between intensity of gap junctional coupling and metastasis, the underlying mechanism of connexin dependent regulation of invasive potential of tumor cells is yet to be determined. In summary, in the initial stages of tumorigenesis, GJ acts as tumor suppressors whereas in migrating tumor cells re-expression of connexins promotes tumor metastasis.

The role of HC in cancer is very limited currently and is an avenue for future research. A recent study showed HC-mediated ATP responses which are triggered by changes of intracellular [Ca^{2+}] in Cx43 expressing glioma cells and primary glial cells (334). The involvement of HC is confirmed with Cx43 gene-silencing and exclusion of other factor-release mechanisms. Changes in the [Ca^{2+}] affect the HC responses. [Ca^{2+}] triggers responses induced by A23187 and glutamate activates a signaling cascade that involves calmodulin (CaM), CaM-dependent kinase II, p38 MAPK, phospholipase A2, arachidonic acid (AA), lipoxygenases, cyclo-oxygenases, reactive oxygen species, nitric oxide and depolarization (334). Similar findings are observed in primary glial cells isolated from rat cortex (334).

5. Connexins and Apoptosis

Though a substantial number of studies suggest a positive correlation between GJIC and apoptosis, contradictory reports point to a protective role of gap junctions against cell death. Evidence for contribution of gap junctions to cell death came from the observation that carbenoxolone and 18-beta-glycyrrhetinic acid, the chemical GJ inhibitors, prevent apoptosis (213;335;336). Further evidence in support of this came from studies where connexin overexpression stimulates cell death (337–343). In contrast to these reports, GJIC chemical inhibitors and connexin mimetic peptides were shown to induce apoptosis (344–346). Extensive studies by several groups demonstrate that the early phases of apoptosis require GJIC, whereas in the later stage this form of communication is greatly reduced among dying cells (164;336;347). Though a number of studies show either protective or stimulating effect of GJIC on cell death, the underlying biochemical messenger(s), which passes through GJs, to mediate these effects is still unknown. In this regard, Ca^{2+} is being considered as a possible death promoting messenger (348;349), however, diffusion of Ca^{2+} through GJs could be limited by its interaction with Ca^{2+} binding proteins. Other possible candidates to promote cell death by connexins could be IP3, cAMP and cGMP as they can pass through GJs (340;350;351). The cell protective effect of GJIC could be possibly mediated by glucose, ATP, ascorbic acid or glutathione as these molecules can pass through GJs (352).

Studies conducted to investigate the role of Cx32 HC in hepatocellular apoptosis have traced the Fas mediated hepatocyte cell death to a contribution of Cx32 HC. Cx32 HC have been shown to play a role in the transition of hepatocyte from apoptotic to necrotic state (167). In another interesting study, a mutant of Cx50 isolated from a child with congenital total cataract promoted cell death but had normal HC function (351). The Cx50 mutant in this study had a glycine at residue 46 replaced with valine (Cx50G46V). Although, no effect on the expression of the mutant at the plasma membrane was noticed, the enhanced HC activity was associated with increased cell death in the HeLa cells where it was expressed. Increased cell death due to Cx50G46V was prevented in presence of high concentration of calcium.

Aberrant HC activity arising from mutations in Cx26 has been a major cause for loss of cell viability and tissue integrity in patients suffering from Keratitis-ichthyosis-deafness (*KID*) *syndrome*, an ectodermal skin disorder. Although, no effect on protein synthesis was noticed in the xenopus oocytes with G12R, N14K, and D50N mutations in Cx26, but an increase in HC currents corresponded to increased cell death (353). Another mutation in Cx26 at the G45E resulted in leaky HC which lead to cell apoptosis in 24 hr of transfection in HEK293 cells and could be partially responsible for hearing impairment (81).

PKC, a protein kinase can reduce the HC opening (354;355) and inhibitors to the PKC like staurosporine (ST) can promote apoptosis of the cell (356). A study showed that the mechanism of ST mediated cell death was attributed to the presence of active HC. ST

reduced the phosphorylation of full length Cx43 transfected in HeLa cells and most of the Cx43 was found on the cell surface. HeLa cells transfected with truncated C terminus of Cx43 lacked the normal phosphorylation sites and even after ST treatment most of the Cx43 was found in the cytosol. When dye uptake was performed on ST treated HeLa cells with Cx43, HeLa cells with truncated Cx43 and HeLa alone, a ten fold increase in the HC activity was noticed in HeLa with Cx43 after treatment with ST. On the other hand, no change in HC activity was observed in HeLa with truncated Cx43 or HeLa alone (357).

Conclusion and Perspective

All these evidences clearly point to the ubiquitous role of GJ and HC in regulating development, differentiation and overall homeostasis of different organ and tissues. Though great advances have been made to understand role of individual connexins in a variety of tissues and cells, the future challenge is to identify specific molecules that pass through the GJ and HC and modulate cellular function. Identification of such molecules would greatly contribute to the development of effective therapeutic means to treat diseases caused by defective or overactive GJ and/or HC function.

The role of gap junctions and hemichannels in various tissues is discussed.

The role of these channels in cell cycle and stem cell development is discussed.

The contribution of these channels to carcinogenesis and apoptosis is discussed.

Acknowledgments

This work was supported by National Institutes of Health Grant EY012085 and Welch Foundation grant AQ-1507 (to J.X.J.).

References

1. Saez JC, Berthoud VM, Branes MC, Martinez AD, Beyer EC. Physiol. Rev. 2003; 83:1359–1400. [PubMed: 14506308]
2. Cruciani V, Mikalsen SO. Biol. Chem. 2007; 388:253–264. [PubMed: 17338632]
3. Goodenough DA, Paul DL. Cold Spring Harb. Perspect. Biol. 2009; 1 a002576.
4. Batra N, Kar R, Jiang JX. Biochim. Biophys. Acta. 2011 **[Epb ahead of print],**
5. Hanner F, Sorensen CM, Holstein-Rathlou NH, Peti-Peterdi J. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2011; 298:R1143–R1155. [PubMed: 20164205]
6. Gershon E, Plaks V, Dekel N. Mol. Cell Endocrinol. 2008; 282:18–25. [PubMed: 18162286]
7. McLachlan E, Shao Q, Laird DW. J. Membrane Biol. 2007; 218:107–121. [PubMed: 17661126]
8. Pointis G, Segretain D. Trends Endocrinol. Metab. 2005; 16:300–306. [PubMed: 16054834]
9. Harris AL. Prog. Biophys. Mol. Biol. 2007; 94:120–143. [PubMed: 17470375]
10. Valiunas V, Polosina YY, Miller H, Potapova IA, Valiuniene L, Doronin S, Mathias RT, Robinson RB, Rosen MR, Cohen IS, Brink PR. J. Physiol. 2005; 568:459–468. [PubMed: 16037090]
11. Neijssen J, Herberts C, Drijfhout JW, Reits E, Janssen L, Neefjes J. Nature. 2005; 434:83–88. [PubMed: 15744304]
12. Sáez JC, Schalper KA, Retamal MA, Orellana JA, Shoji KF, Bennett MV. Exp. Cell Res. 2010; 316:2377–2389. [PubMed: 20595004]
13. Dale N. J. Physiol. 2008; 586:2429–2436. [PubMed: 18356200]
14. Ye ZC, Wyeh MS, Baltan-Tekkok S, Ransom BR. J. Neurosci. 2003:3588–3596. [PubMed: 12736329]

15. Bruzzone S, Guida L, Zocchi E, Franco L, De Flora A. FASEB J. 2000; 15:10–12. [PubMed: 11099492]
16. Cherian PP, Siller-Jackson AJ, Gu S, Wang X, Bonewald LF, Sprague E, Jiang JX. Mol. Biol. Cell. 2005; 16:3100–3106. [PubMed: 15843434]
17. Bergoffen J, Scherer SS, Wang S, Scott MO, Bone LJ, Paul DL, Chen K, Lensch MW, Chance PF, Fischbeck KH. Science. 1993; 262:2039–2042. [PubMed: 8266101]
18. Kelsell DP, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G, Mueller RF, Leigh IM. Nature. 1997; 387:80–83. [PubMed: 9139825]
19. Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, Osborn AH, Dahl HH, Middleton A, Houseman MJ, Dodé C, Marlin S, Boulila-ElGaied A, Grati M, Ayadi H, BenArab S, Bitoun P, Lina-Granade G, Godet J, Mustapha M, Loiselet J, El-Zir E, Aubois A, Joannard A, Petit C. Hum. Mol. Genet. 1997; 6:2173–2177. [PubMed: 9336442]
20. Uhlenberg B, Schuelke M, Ruschendorf F, Ruf N, Kaindl AM, Henneke M, Thiele H, Stoltenburg-Didnger G, Aksu F, Topaloglu H, Nurnberg P, Hubner C, weschke B, Gartner J. Am. J. Hum. Genet. 2004; 75:251–260. [PubMed: 15192806]
21. Gong X, Cheng C, Xia C. J. Memb. Biol. 2007; 218:9–12.
22. Jiang JX. Curr. Mol. Med. 2010; 10:851–863. [PubMed: 21091421]
23. Paznekas WA, Boyadjiev SA, Shapiro RE, Daniels O, Wollnik B, Keegan CE, Innis JW, Dinulos MB, Christian C, Hannibal MC, Jabs EW. Am. J. Hum. Genet. 2003; 72:408–418. [PubMed: 12457340]
24. Schalper KA, Orellana JA, Berthoud VM, Sáez JC. Curr. Vasc. Pharmacol. 2009; 7:486–505. [PubMed: 19485891]
25. Panchin Y, Kelmanson I, Matz M, Lukyanov K, Usman N, Lukyanov S. Curr. Biol. 2000; 10:R473–R474. [PubMed: 10898987]
26. Lai CP, Bechberger JF, Thompson RJ, macVicar BA, Bruzzone R, Naus CC. Cancer Res. 2007; 67:1545–1554. [PubMed: 17308093]
27. Litvin O, Tiunova A, Connell-Alberts Y, Panchin Y, Baranova A. J. Cell Mol. Med. 2006; 10:613–634. [PubMed: 16989724]
28. Shestopalov VI, Panchin Y. Cell Mol. Life Sci. 2008; 65:376–394. [PubMed: 17982731]
29. van Kempen MJ, Ten Velde I, Wessels A, Oosthoek PW, Gros D, Jongsma HJ, Moorman AF, Lamers WH. Microsc. Res. Tech. 1995; 31:420–436. [PubMed: 8534903]
30. Vozzi C, Dupont E, Coppen SR, Yeh HI, Severs NJ. J. Mol. Cell Cardiol. 1999; 31:991–1003. [PubMed: 10336839]
31. Severs NJ, Rothery S, Dupont E, Coppen SR, Yeh HI, Ko YS, Matsushita T, Kaba R, Halliday D. Microsc. Res. Tech. 2001; 52:301–322. [PubMed: 11180622]
32. Reaume AG, De Sousa PA, Kulkarni S, Langille BL, Zhu D, Davies TC, Juneja SC, Kidder GM, Rossant J. Science. 1995; 267:1831–1834. [PubMed: 7892609]
33. Leaf DE, Feig JE, Vasquez C, Riva PL, Yu C, Lader JM, Kontogenorgis A, Baron EL, Peters NS, Fisher EA, Gutstein DE, Morley GE. Circ. Res. 2008; 103:1001–1008. [PubMed: 18599871]
34. Nishii K, Kumai M, Egashira K, Miwa T, Hashizume K, Miyano Y, Shibata Y. Cell Commun. Adhes. 2003; 10:365–369. [PubMed: 14681043]
35. Gu H, Smith FC, Taffet SM, Delmar M. Circ. Res. 2003; 93:201–206. [PubMed: 12842919]
36. Krüger O, Maxeiner S, Kim JS, Van Rijen HV, de Bakker JM, Eckardt D, Tiemann K, Lewalter T, Ghanem A, Lüderitz B, Willecke K. J. Mol. Cell. Cardiol. 2006; 41:787–797. [PubMed: 16919680]
37. Britz-Cunningham SH, Shah MM, Zuppan CW, Fletcher WH. New Engl. J. Med. 1995; 332:1323–1329. [PubMed: 7715640]
38. Dasgupta C, Martinez AM, Zuppan CW, Shah MM, Bailey LL, Fletcher WH. Mutat. Res. 2001; 479:173–186. [PubMed: 11470490]
39. Debrus S, Tuffery S, Matsuoka R, Galal O, Sarda P, Sauer U, Bozio A, Tanman B, Toutain A, Claustres M, Le Paslier D, Bouvagnet P. J. Mol. Cell Cardiol. 1997; 29:1423–1431. [PubMed: 9201627]
40. Gebbia M, Towbin JA, Casey B. Circulation. 1996; 94:1909–1912. [PubMed: 8873667]

41. Garcia-Dorado D, Rodriguez-Sinovas A, Ruiz-Meana M. Cardiovasc. Res. 2004; 61:386–401. [PubMed: 14962471]
42. Garcia-Dorado D, Inserte J, Ruiz-Meana M, González MA, Solares J, Juliá M, Barrabés JA, Soler-Soler J. Circulation. 1997; 96:3579–3586. [PubMed: 9396458]
43. Ruiz-Meana M, Rodriguez-Sinovas A, Cabestrero A, Boengler K, Heusch G, Garcia-Dorado D. Cardiovasc. Res. 2008; 77:325–333. [PubMed: 18006437]
44. Schwanke U, Konietzka I, Duschin A, Li X, Schulz R, Heusch G. Am. J. Physiol. Heart Circ. Physiol. 2002; 283:H1740–H1742. [PubMed: 12234831]
45. Kanno S, Kovacs A, Yamada KA, Saffitz JE. J. Am. Coll. Cardiol. 2003; 41:681–686. [PubMed: 12598083]
46. Totzeck A, Boengler K, van de Sand A, Konietzka I, Gres P, Garcia-Dorado D, Heusch G, Schulz R. Am. J. Physiol. Heart Circ. Physiol. 2008; 295:H2106–H2112. [PubMed: 18835920]
47. Boengler K, Stahlhofen S, van de Sand A, Gres P, Ruiz-Meana M, Garcia-Dorado D, Heusch G, Schulz R. Basic Res. Cardiol. 2009; 104:141–147. [PubMed: 19242638]
48. Miro-Casas E, Ruiz-Meana M, Agullo E, Stahlhofen S, Rodriguez-Sinovas A, Cabestrero A, Jorge I, Torre I, Vazquez J, Boengler K, Schulz R, Heusch G, Garcia-Dorado D. Cardiovasc. Res. 2009; 83:747–756. [PubMed: 19460776]
49. Costa AD, Carlid KD. Am. J. Physiol. Heart Circ. Physiol. 2008; 295:H874–H882. [PubMed: 18586884]
50. Murphy E. Circ. Res. 2004; 94:7–16. [PubMed: 14715531]
51. Danik SB, Liu F, Zhang J, Suk HJ, Morley GE, Fishman GI, Gutstein DE. Circ. Res. 2004; 95:1035–1041. [PubMed: 15499029]
52. Yamada KA, Rogers JG, Sundset R, Steinberg TH, Saffitz JE. J. Cardiovasc. Electrophysiol. 2003; 14:1205–1212. [PubMed: 14678136]
53. Betsuyaku T, Nnebe NS, Sundset R, Patibandla S, Krueger CM, Yamada KA. Am. J. Physiol. Heart Circ. Physiol. 2006; 290:H163–H171. [PubMed: 16126808]
54. Dupont E, Matsushita T, Kaba RA, Vozzi C, Coppen SR, Khan N, Kaprielian R, Yacoub MH, Severs NJ. J. Mol. Cell Cardiol. 2001; 33:359–371. [PubMed: 11162139]
55. Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. Nat. Med. 2007; 13:486–491. [PubMed: 17401374]
56. Bruce AF, Rothery S, Dupont E, Severs NJ. Cardiiovasc. Res. 2008; 77:757–765.
57. Oxford EM, Musa H, Maass K, Coombs W, Taffet SM, Delmar M. Circ. Res. 2007; 101:703–711. [PubMed: 17673670]
58. John SA, Kondo R, Wang S-Y, Goldhaber JI, Weiss JN. J. Biol. Chem. 1999; 274:236–240. [PubMed: 9867835]
59. Kondo RP, Wang S-Y, John SA, Weiss JN, Goldhaber JI. J. Mol. Cell Cardiol. 2000; 32:1859–1872. [PubMed: 11013130]
60. Beardslee MA, Lerner DL, Tadros PN, Laing JG, Beyer EC, Yamada KA, Kléber AG, Schuessler RB, Saffitz JE. Circ. Res. 2000; 87:656–662. [PubMed: 11029400]
61. Armstrong SC, Ganote CE. J. Mol. Cell Cardiol. 1992; 24:869–884. [PubMed: 1331472]
62. Weinbrenner C, Baines CP, Liu GS, Armstrong SC, Ganote CE, Walsh AH, Honkanen RE, Cohen MV, Downey JM. Circulation. 1998; 98:899–905. [PubMed: 9738645]
63. Schulz R, Gres P, Skyschally A, Duschin A, Belosjorow S, Konietzka I, Heusch G. FASEB J. 2003; 17:1355–1357. [PubMed: 12759340]
64. Li F, Sugishita K, Su Z, Ueda I, Barry WH. J. Mol. Cell Cardiol. 2001; 33:2145–2155. [PubMed: 11735261]
65. Kunugi S, Iwabuchi S, Matsuyama D, Okajima T, Kawahara K. Biochem. Biophys. Res. Commun. 2011; 416:409–415. [PubMed: 22133679]
66. John S, Cesario D, Weiss JN. Acta Physiol. Scand. 2003; 179:23–31. [PubMed: 12940935]
67. Shintani-Ishida K, Uemura K, Yoshida K. Am. J. Physiol. Heart Circ. Physiol. 2007; 293:H1714–H1720. [PubMed: 17557925]

68. Hawat G, Benderdour M, Rousseau G, Baroudi G. Pflugers Arch. 2010; 2010:583–592. [PubMed: 20514543]
69. Johansen D, Cruciani V, Sundset R, Ytrehus K, Mikalsen SO. Cell Physiol. Biochem. 2011; 28:103–114. [PubMed: 21865853]
70. Martinez AD, Acuña R, Figueroa V, Maripillan J, Nicholson B. Antioxid. Redox. Signal. 2009; 11:309–322. [PubMed: 18837651]
71. Kelsell DP, Di WL, Houseman MJ. Am. J. Hum. Genet. 2001; 68:559–568. [PubMed: 11179004]
72. Petit C, Levilliers J, Hardelin JP. Annu. Rev. Genet. 2001; 35:589–646. [PubMed: 11700295]
73. Thönnissen E, Rabionet R, Arbonès ML, Estivill X, Willecke K, Ott T. Hum. Genet. 2002; 111:190–197. [PubMed: 12189493]
74. Kikuchi T, Adams JC, Miyabe Y, So E, Kobayashi T. Med. Electron Microsc. 2000; 33:51–56. [PubMed: 11810458]
75. Gossman DG, Zhao HB. Cell Commun. Adhes. 2008; 15:305–315. [PubMed: 18979296]
76. Zhao HB. Eur. J. Neurosci. 2005; 21:1859–1868. [PubMed: 15869481]
77. Anselmi F, Hernandez VH, Crispino G, Seydel A, Ortolano S, Roper SD, Kessaris N, Richardson W, Rickheit G, Filippov MA, Monyer H, Mammano F. Proc. Natl. Acad. Sci. 2008; 105:18770–18775. [PubMed: 19047635]
78. Sánchez HA, Mese G, Srinivas M, White TW, Verselis VK. J. Gen. Physiol. 2010; 136:47–62. [PubMed: 20584891]
79. Griffith AJ, Yang Y, Pryor SP, Park HJ, Jabs EW, Nadol JBJ, Russell LJ, Wasseman DI, Richard G, Adams JC, Merchant SN. Laryngoscope. 2006; 116:1404–1408. [PubMed: 16885744]
80. Janecke AR, Hennies HC, Günther B, Gansl G, Smolle J, Messmer EM, Utermann G, Rittinger O. Am. J. Med. Genet. 2005; 133A:128–131. [PubMed: 15633193]
81. Stong BC, Chang Q, Ahmad S, Lin X. Larynogoscope. 2006; 116:2205–2210.
82. Tang W, Ahmad S, Shestopalov VI, Lin X. Neuroreport. 2008; 19:1253–1257. [PubMed: 18695503]
83. Wang X-H, Streeter M, Liu Y-P, Zhang H-B. J. Comp. Neurol. 2009; 512:336–346. [PubMed: 19009624]
84. Hanner F, Sorensen CM, Holstein-Rathlou NH, Peti-Peterdi J. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2010; 298:R1143–R1155. [PubMed: 20164205]
85. Arensbak B, Mikkelsen HB, Gustafsson F, Christensen T, Holstein-Rathlou NH. Histochem. Cell Biol. 2001; 115:479–487. [PubMed: 11455448]
86. Haefliger JA, Demotz S, Braissant O, Suter E, Waeber B, Nicod P, Meda P. Kidney Int. 2001; 60:190–201. [PubMed: 11422751]
87. Hwan Seul K, Beyer EC. Microvasc. Res. 2000; 59:140–148. [PubMed: 10625581]
88. Zhang J, Hill CE. Kidney Int. 2005; 68:1171–1185. [PubMed: 16105048]
89. Kühn K, Reale E. Cell Tissue Res. 1975; 160:193–205. [PubMed: 1149116]
90. Pricam G, Humbert F, Perrelet A, Orci L. J. Cell Biol. 1974; 63:349–354. [PubMed: 4421621]
91. Mink D, Schiller A, Kriz W, Taugner R. Cell Tissue Res. 1984; 236:567–576. [PubMed: 6380740]
92. Taugner R, Schiller A, Kaissling B, Kriz W. Cell Tissue Res. 1978; 186:279–285. [PubMed: 627020]
93. Sawai K, Mukoyama M, Mori K, Yokoi H, Koshikawa M, Yoshioka T, Takeda R, Sugawara A, Kuwahara T, Saleem MA, Ogawa O, Nakao K. Nephrol. Dial. Transplant. 2006; 21:2472–2477. [PubMed: 16820374]
94. Figueroa XF, Duling BR. Antioxid. Redox Signal. 2009; 11:251–266. [PubMed: 18831678]
95. de Wit C, Roos F, Bolz SS, Pohl U. Physiol. Genomics. 2003; 13:169–177. [PubMed: 12700362]
96. Chaytor AT, Evans WH, Griffith TM. J. Physiol. 1998; 508:561–573. [PubMed: 9508817]
97. Dora KA, Martin PE, Chaytor AT, Evans WH, Garland CJ, Griffith TM. Biochem. Biophys. Res. Commun. 1999; 524:27–31. [PubMed: 9920727]
98. Hutcheson IR, Chaytor AT, Evans WH, Griffith TM. Circ. Res. 1999; 84:53–63. [PubMed: 9915774]
99. Griffith TM, Chaytor AT, Edwards DH. Pharmacol. Res. 2004; 49:551–564. [PubMed: 15026033]

100. Kurtz L, Schweda F, de Wit C, Kriz W, Witzgall R, Warth R, Sauter A, Kurtz A, Wagner C. J. Am. Soc. Nephrol. 2007; 18:1103–1111. [PubMed: 17329574]
101. Krattinger N, Capponi A, Mazzolai L, Aubert JF, Caille D, Nicod P, Waeber G, Meda P, Haefliger JA. Kidney Int. 2007; 72:814–822. [PubMed: 17622273]
102. Hanner F, von Malzahn J, Maxeiner S, Toma I, Sipos A, Krüger O, Willecke K, Peti-Peterdi J. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2008; 295:R371–R380. [PubMed: 18579650]
103. Haefliger JA, Krattinger N, Martin D, Pedrazzini T, Capponi A, Döring B, Plum A, Charollais A, Willecke K, Meda P. J. Clin. Invest. 2006; 116:405–413. [PubMed: 16440062]
104. Liao Y, Day KH, Damon DN, Duling BR. Proc. Natl. Acad. Sci. 2001; 98:9989–9994. [PubMed: 11481448]
105. Theis M, de Wit C, Schlaeger TM, Eckardt D, Krüger O, Döring B, Risau W, Deutsch U, Pohl U, Willecke K. Genesis. 2001; 29:1–13. [PubMed: 11135457]
106. McCulloch F, Chambrey R, Eladari D, Peti-Peterdi J. Am. J. Physiol. Renal. Physiol. 2005; 289:F1304–F1312. [PubMed: 16077080]
107. Stoessel A, Himmerkus N, Bleich M, Bachmann S, Theilig F. Am. J. Physiol. Renal Physiol. 2010; 298:F216–F223. [PubMed: 19828678]
108. Silverstein DM, Urban M, Gao Y, Mattoo TK, Spray DC, Rozental R. Pediatr. Nephrol. 2001; 16:467–471. [PubMed: 11420908]
109. White TW, Paul DL. Annu. Rev. Physiol. 1999; 61:283–310. [PubMed: 10099690]
110. Willecke K, Kirchhoff S, Plum A, Temme A, Thönnissen E, Ott T. Novartis Found. Symp. 1999; 219:76–88. [PubMed: 10207899]
111. Takenaka T, Inoue T, Kanno Y, Okada H, Hill CE, Suzuki H. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2008; 294:R1–R11. [PubMed: 17928514]
112. Just A, Kurtz L, de Wit C, Wagner C, Kurtz A, Arendshorst WJ. J. Am. Soc. Nephrol. 2009; 20:1577–1585. [PubMed: 19443640]
113. Vergara L, Bao X, Bello-Reuss E, Reuss L. Acta. Physiol. Scand. 2003; 179:33–38. [PubMed: 12940936]
114. Vergara L, Bao X, Cooper M, Bello-Reuss E, Reuss L. J. Membrane Biol. 2003; 196:173–184. [PubMed: 14724743]
115. Goodenough, DA. The crystalline lens: a system networked by gap junctional intercellular communication. In: Gilula, NB., editor. Seminars in Cell Biology. London: Sauders Scientific Pub./Academic Press; 1992.
116. Beyer EC, Paul DL, Goodenough DA. J. Cell Biol. 1987; 105:2621–2629. [PubMed: 2826492]
117. Jiang JX, White TW, Goodenough DA. Dev. Biol. 1995; 168:649–661. [PubMed: 7729595]
118. Paul DL, Ebihara L, Takemoto LJ, Swenson KI, Goodenough DA. J. Cell Biol. 1991; 115:1077–1089. [PubMed: 1659572]
119. White TW, Bruzzone R, Goodenough DA, Paul DL. Mol. Biol. Cell. 1992; 3:711–720. [PubMed: 1325220]
120. Gong X, Li E, Klier G, Huang Q, Wu Y, Lei H, Kumar NM, Horwitz J, Gilua NB. Cell. 1997; 91:833–843. [PubMed: 9413992]
121. White TW, Goodenough DA, Paul DL. J. Cell Biol. 1998; 143:815–825. [PubMed: 9813099]
122. Baruch A, Greenbaum D, Levy ET, Nielsen PA, Gilula NB, Kumar NM, Bogyo M. J. Biol. Chem. 2001; 276:28999–29006. [PubMed: 11395508]
123. Gu S, Yu XS, Yin X, Jiang JX. Invest. Ophthalmol. Vis. Sci. 2003; 44:2103–2111. [PubMed: 12714649]
124. Sellitto C, Li L, White TW. Invest. Ophthal. Vis. Sci. 2004; 45:3196–3202. [PubMed: 15326140]
125. BAnks EA, Yu XS, Shi Q, Jiang JX. J. Cell Sci. 2007; 120:3602–3612. [PubMed: 17895360]
126. Baldo G, Gong X, Martinez-Wittinghan FJ, Kumar N, Gilula NB, Mathias RT. J. Gen. Physiol. 2001; 118:447–456. [PubMed: 11696604]
127. White TW. Science. 2002; 295:319–320. [PubMed: 11786642]
128. Gao Y, Spray DC. Invest. Ophthal. Vis. Sci. 1998; 37:1198–1209. [PubMed: 9620080]

129. White TW, Sellitto C, Paul DL, Goodenough DA. Invest. Ophthalmol. Vis. Sci. 2001; 42:2916–2923. [PubMed: 11687537]
130. Bao L, Sachs F, Dahl G. Am. J. Physiol. (Cell Physiol.). 2004; 287:C1389–C1395. [PubMed: 15475518]
131. Zhang X, Zou T, Liu Y, Qi Y. Biol. Chem. 2006; 387:595–601. [PubMed: 16740131]
132. Srinivas M, Calderon DP, Kronengold J, Verselis VK. J. Gen. Physiol. 2006; 127:67–75. [PubMed: 16380444]
133. Zampighi GA. Cell Commun. Adhes. 2003; 10:265–270. [PubMed: 14681027]
134. Liu J, Ek Vitorin JF, Weintraub ST, Gu S, Shi Q, Burt JM, Jiang JX. J. Biol. Chem. 2011; 286:16914–16928. [PubMed: 21454606]
135. Revel JP, Karnovsky MJ. J. Cell Biol. 1967; 33:C7–C12. [PubMed: 6036535]
136. Goodenough DA. J. Cell Biol. 1974; 61:557–563. [PubMed: 4363961]
137. Cascio M, Kumar NM, Safarik R, Gilula NB. J. Biol. Chem. 1995; 270:18643–18648. [PubMed: 7629194]
138. Neveu MJ, Hully JR, Babcock KL, Vaughan J, Hertzberg EL, Nicholson BJ, Paul DL, Pitot HC. Hepatology. 1995; 22:202–212. [PubMed: 7601414]
139. Shiojiri N, NIwa T, Sugiyama Y, Koike T. Cell Tissue Res. 2006; 324:547–552. [PubMed: 16505993]
140. Zhang J-T, Nicholson BJ. J. Cell Biol. 1989; 109:3391–3401. [PubMed: 2557354]
141. Traub O, Druge M, Willecke K. Proc. Natl. Acad. Sci. (USA). 1983; 80:755–759. [PubMed: 6298773]
142. Dermietzel R, Yancey SB, Traub O, Willecke K, Revel JP. J. Cell Biol. 1987; 105:1925–1934. [PubMed: 2822729]
143. Fladmark KE, Gjertsen BT, Molven A, Mellgren G, Vintermyr OK, Døskeland SO. Hepatology. 1997; 25:847–855. [PubMed: 9096587]
144. Kren BT, Kumar NM, Wang S, Gilula NB, Steer CJ. J. Cell Biol. 1993; 123:707–718. [PubMed: 8227133]
145. Meyer DJ, Yancey SB, Revel JP. Journal of Cell Biology. 1981; 91:505–523. [PubMed: 7309793]
146. Temme A, Ott T, Dombrowski F, Willecke K. J. Hepatol. 2000; 32:627–635. [PubMed: 10782912]
147. Dagli ML, Yamasaki H, Krutovskikh V, Omori Y. Carcinogenesis. 2004; 25:483–492. [PubMed: 14688024]
148. Koffler L, Roshong S, Kyu PI, Cesen-Cummings K, Thompson DC, Dwyer-Nield LD, Rice P, Mamay C, Malkinson AM, Ruch RJ. J. Cell Biochem. 2000; 79:347–354. [PubMed: 10972973]
149. Yano T, Yamasaki H. Mol. Carcinog. 2001; 31:101–109. [PubMed: 11429787]
150. Paku S, Nagy P, Kopper L, Thorgeirsson SS. Hapatology. 2004; 39:1353–1361.
151. Zhang M, Thorgeirsson SS. Exp. Cell Res. 1994; 213:37–42. [PubMed: 7517369]
152. Yang J, Ichikawa A, Tsuchiya T. Biochem. Biophys. Res. Commun. 2003; 307:80–85. [PubMed: 12849984]
153. Stümpel F, Ott T, Willecke K, Jungermann K. Hepatology. 1998; 28:1616–1620. [PubMed: 9828226]
154. Nathanson MH, Rios-Velez L, Burgstahler AD, Mennone A. Gastroenterology. 1999; 116:1176–1183. [PubMed: 10220510]
155. Hamilton GA, Jolley SL, Gilbert D, Coon DJ, Barros S, Lecluyse EL. Cell Tissue Res. 2001; 306:85–99. [PubMed: 11683185]
156. Neveu MJ, Babcock KL, Hertzberg EL, Paul DL, Nicholson BJ, Pitot HC. Cancer Research. 1994; 54:3145–3152. [PubMed: 8205533]
157. Shoda T, Mitsumori K, Onodera H, Tyoda K, Uneyama C, Imazawa T, Hirose M. Arch. Toxicol. 1999; 73:373–380. [PubMed: 10550479]
158. Shoda T, Mitsumori K, Onodera H, Toyoda K, Uneyama C, Takada K, Hirose M. Toxicol. Pathol. 2000; 28:540–547. [PubMed: 10930040]
159. Chipman JK, Mally A, Edwards GO. Toxicol. Sci. 2003; 71:146–153. [PubMed: 12563100]

160. Nakata Y, Iwai M, Kimura S, Shimazu T. J. Hepatol. 1996; 25:529–537. [PubMed: 8912153]
161. Asamoto M, Hokaiwado N, Murasaki T, Shirai T. Hepatology. 2004; 40:205–210. [PubMed: 15239104]
162. Muramatsu A, Iwai M, Morikawa T, Tanaka S, Mori T, Harada Y, Okanoue T. Carcinogenesis. 2002; 23:351–358. [PubMed: 11872644]
163. Albright CD, Kuo J, Jeong S. Exp. Mol. Pathol. 2001; 71:34–39. [PubMed: 11502095]
164. Wilson MR, Close TW, Trosko JE. Exp. Cell Res. 2000; 254:257–268. [PubMed: 10640424]
165. Ogasawara J, Watanabe-Fukunaga R, Adachi M, Matsuzawa A, Kasugai T, Kitamura Y, Itoh N, Suda T, Nagata S. Nature. 1993; 364:806–809. [PubMed: 7689176]
166. Rouquet N, Carlier K, Briand P, Wiels J, Joulin V. Biochem. Biophys. Res. Commun. 1996; 229:27–35. [PubMed: 8954079]
167. Vinken M, Decrock E, de Vuyst E, De Bock M, Vandenbroucke RE, De Geest BG, Demeester J, Sanders NN, Vanhaecke T, Leybaert L, Rogiers V. Cell Mol. Life Sci. 2010; 67:907–918. [PubMed: 19960225]
168. Vinken M, Decrock E, Vanhaecke T, Leybaert L, Rogiers V. Toxicol. Sci. 2012; 125:175–186. [PubMed: 22003192]
169. Sanderson MJ, Chow I, Dirksen ER. Am. J. Physiol. 1988; 254:C63–C74. [PubMed: 3337222]
170. Kuebler WM, Parthasarathi K, Lindert J, Bhattacharya J. J. Appl. Physiol. 2007; 102:1255–1264. [PubMed: 17095639]
171. Ichimura H, Parthasarathi K, Lindert J, Bhattacharya J. Am. J. Physiol. Lung Cell Mol. Physiol. 2006; 291:L596–L601. [PubMed: 16698857]
172. Beyer EC, Reed KE, Westphale EM, Kanter HL, Larson DM. J. Membrane. Biol. 1992; 127:69–76. [PubMed: 1328644]
173. Nakamura K, Inai T, Nakamura K, Shibata Y. Arch. Histol. Cytol. 1999; 62:27–37. [PubMed: 10223740]
174. Traub O, Hertlein B, Kasper M, Eckert R, Krisciukaitis A, Hülser D, Willecke K. Eur. J. Cell Biol. 1998; 77:313–322. [PubMed: 9930656]
175. Johnson LN, Koval M. Antioxid. Redox Signal. 2009; 11:355–367. [PubMed: 18816185]
176. Parthasarathi K, Ichimura H, Monma E, Lindert J, Quadri S, Issekutz A, Bhattacharya J. J. Clin. Invest. 2006; 116:2193–2200. [PubMed: 16878174]
177. Kwak BR, Mulhaupt F, Veillard N, Gros DB, Mach F. Arterioscler. Thromb. Vasc. Biol. 2002; 22:225–230. [PubMed: 11834520]
178. Derouette JP, Desplantez T, Wong CW, Roth I, Kwak BR, Weingart R. J. Mol. Cell Cardiol. 2009; 46:499–507. [PubMed: 19166859]
179. Wong CW, Christen T, Roth I, Chadjichristos CE, Derouette JP, Foglia BF, Chanson M, Goodenough DA, Kwak BR. Nat. Med. 2006; 12:950–954. [PubMed: 16862155]
180. Ransford GA, Fregien N, Qiu F, Dahl G, Conner GE, Salathe M. Am. J. Respir. Cell Mol. Biol. 2009; 41:525–534. [PubMed: 19213873]
181. Schneeberger EE, Lynch RD. Am. J. Physiol. 1992; 262:L647–L661. [PubMed: 1616050]
182. Nagasawa K, Chiba H, Fujita H, Kojima T, Saito T, Endo T, Sawada N. J. Cell Physiol. 2006; 208:123–132. [PubMed: 16547974]
183. Kojima T, Spray DC, Kokai Y, Chiba H, Mochizuki Y, Sawada N. Exp. Cell Res. 2002; 276:40–51. [PubMed: 11978007]
184. Koval M, Billaud M, Straub AC, Johnstone SR, Zarbock A, Duling BR, Isakson BE. Am. J. Pathol. 2011; 178:2536–2546. [PubMed: 21641379]
185. Figueroa XF, Paul DL, Simon AM, Goodenough DA, Day KH, Damon DH, Duling BR. Circ. Res. 2003; 92:793–800. [PubMed: 12637364]
186. Chatterjee S, Baeter S, Bhattacharya J. Am. J. Physiol. Lung Cell Mol. Physiol. 2007; 293:L517–L519. [PubMed: 17545487]
187. Lee SW, Tomasetto C, Paul DL, Keyomarsi K, Sager R. J. Cell Biol. 1992; 118:1213–1222. [PubMed: 1324944]

188. Tomasetto C, Neveu MJ, Daley J, Horan PK, Sager R. J. Cell Biol. 1993; 122:157–167. [PubMed: 8391000]

189. Pozzi A, Risek B, Kiang DT, Gilula NB, Kumar NM. Experimental Cell Research. 1995; 220:212–219. [PubMed: 7664837]

190. Monaghan P, Moss DW. Cell Biol. Internat. 1996; 20:121–125.

191. Monaghan P, Clarke C, Perusinghe NP, Moss DW, Chen XY, Evans WH. Exp. Cell Res. 1996; 223:29–38. [PubMed: 8635493]

192. Laird DW, Fistouris P, Batist G, Alpert L, Huynh HT, Carystinos GD, Alaoui-Jamali MA. Cancer Res. 1999; 59:4104–4110. [PubMed: 10463615]

193. Monaghan P, Perusinghe N, Carlile G, Evans WH. J. Histochem. Cytochem. 1994; 42:931–938. [PubMed: 8014476]

194. Talhouk RS, Elble RC, Bassam R, Daher M, Sfeir A, Mosleh LA, El-Khoury H, Hamoui S, Pauli BU, El-Sabban ME. Cell Tissue Res. 2005; 319:49–59. [PubMed: 15517403]

195. Bry C, Maass K, Miyoshi K, Willecke K, Ott T, Robinson GW, Hennighausen L. Dev. Biol. 2004; 267:418–429. [PubMed: 15013803]

196. Ayad WA, Locke D, Koreen IV, Harris AL. J. Biol. Chem. 2006; 281:16727–16739. [PubMed: 16601118]

197. Locke D, Perusinghe N, Newman T, Jayatilake H, Evans WH, Monaghan P. J. Cell Physiol. 2000; 183:228–237. [PubMed: 10737898]

198. Locke D, Stein T, Davies C, Morris J, Harris AL, Evans WH, Monaghan P, Gusterson B. Exp. Cell Res. 2004; 298:643–660. [PubMed: 15265710]

199. Lambe T, Finlay D, Murphy M, Martin F. Cell Biol. Int. 2006; 30:472–479. [PubMed: 16630728]

200. Plum A, Hallas G, Magin T, Dombrowski F, Hagendorff A, Schumacher B, Wolpert C, Kim J-S, Hamers WH, Evert M, Meda P, Traub O, Willecke K. Curr. Biol. 2000; 10:1083–1091. [PubMed: 10996788]

201. El-Sabban ME, Abi-Mosleh LF, Talhouk RS. J. Mammary Gland Biol. Neoplasia. 2003; 8:463–473. [PubMed: 14985641]

202. Naus CC, Bani-Yaghoub M. Cell Biol. Int. 1998; 22:751–763. [PubMed: 10873289]

203. Rozental R, Morales M, Mehler MF, Urban M, Kremer M, Dermietzel R, Kessler JA, Spray DC. J. Neurosci. 1998; 8:1753–1762. [PubMed: 9465000]

204. Nadarajah B, Parmavelas JG. Novartis Found. Symp. 1999; 219:157–170. [PubMed: 10207903]

205. Talhouk RS, Zeinieh MP, Mikati MA, El-Sabban ME. Prog. Neurobiol. 2008; 84:57–76. [PubMed: 18006137]

206. Peinado A, Yuste R, Katz LC. Neuron. 1993; 10:103–114. [PubMed: 8427699]

207. Fushiki S, Perez Velazquez JL, Zhang L, Bechberger JF, Carlen PL, Naus CC. J. Neurophathol Exp. Neurol. 2003; 62:304–314.

208. Naus CC, Bani-Yaghoub M, Rushlow W, Bechberger JF. Adv. Exp. Med. Biol. 1999; 468:373–381. [PubMed: 10635043]

209. Elias LAB, Wang DD, Kriegstein AR. Nature. 2007; 448:901–907. [PubMed: 17713529]

210. Balice-Gordon RJ, Bone LJ, Scherer SS. J. Cell Biol. 1998; 142:1095–1104. [PubMed: 9722620]

211. Frantseva MV, Koharovtseva L, Perez Velazquez JL. J. Cereb. Blood Flow Metab. 2002; 22:453–462. [PubMed: 11919516]

212. Frantseva MV, Kokarovtseva L, Naus CG, Carlen PL, MacFabe D, Perez Velazquez JL. J. Neurosci. 2002; 22:644–653. [PubMed: 11826094]

213. de Pina-Benabou MH, Szostak V, Kyrozia A, Rempe D, Uziel D, Urban-Maldonado M, Benabou S, Spray DC, Federoff HJ, Stanton PK, Rozental R. Stroke. 2005; 36:2232–2237. [PubMed: 16179575]

214. Rawanduzy A, Hansen A, Hansen TW, Nedergaard M. J. Neurosurg. 1997; 87:916–920. [PubMed: 9384404]

215. Rami A, Volkmann T, Winckler J. Exp. Neurol. 2001; 170:297–304. [PubMed: 11476596]

216. Contreras JE, Sanchez HA, Veliz LP, Bukauskas FF, Bennett MV, Saez JC. Brain Res. Brain Res. Rev. 2004; 2004:290–303. [PubMed: 15572178]

217. Retamal MA, Cortés CJ, Reuss L, Bennett MV, Sáez J. Proc. Nat. Acad. Sci. (USA). 2006; 103:4475–4480. [PubMed: 16537412]
218. suadicani SO, Brosnan CF, Scemes E. J. Neurosci. 2006; 26:1378–1385. [PubMed: 16452661]
219. Deans MR, Gibson JR, Selllitto C, Connors BW, Paul DL. Neuron. 2001; 31:477–485. [PubMed: 11516403]
220. Belluardo N, Trovato-Salinaro A, Mudò G, Hurd YL, Condorelli DF. J. Neurosci. Res. 1999; 57:740–752. [PubMed: 10462698]
221. Al-Ubaidi MR, White TW, Ripps H, Poras I, Avner P, Gomès D, Bruzzone R. J. Neurosci. Res. 2000; 59:813–826. [PubMed: 10700019]
222. Schock SC, Leblanc D, Hakim AM, Thompson CS. Biochem. Biophys. Res. Commun. 2008; 368:138–144. [PubMed: 18211823]
223. Valiunas V. J. Gen. Physiol. 2002; 119:147–164. [PubMed: 11815665]
224. Nagy JI, Patel D, Ochalski PA, Stelmack GL. Neuroscience. 1999; 88:447–468. [PubMed: 10197766]
225. Lautermann J, ten Cate WJ, Altenhoff P, Grümmer R, Traub O, Frank H, Jahnke K, Winterhager E. Cell Tissue Res. 1998; 294:415–420. [PubMed: 9799458]
226. Rabionet R, Gasparini P, Estivill X. Hum. Mutat. 2000; 16:190–202. [PubMed: 10980526]
227. Essenfelder GM, Bruzzone R, Lamartine J, Charollais A, Blanchet-Bardon C, Barbe MT, Meda P, Waksman G. Hum. Mo. Genet. 2004; 13:1703–1714.
228. Baranova A, Ivanov D, Petrash N, Pestova A, Skoblov M, Kelmanson I, Shagin D, Nazarenko S, Geraymovych E, Litvin O, Tiunova A, Born TL, Usman N, Staroverov D, Lukyanov S, Panchin Y. Genomics. 2004; 83:706–716. [PubMed: 15028292]
229. Penuela S, Bhalla R, Gong XQ, Cowan KN, Celetti SJ, Cowan BJ, Bai D, Shao Q, Laird DW. J. Cell Sci. 2007; 120:3772–3783. [PubMed: 17925379]
230. Ray A, Zoidl G, Weickert S, Wahle P, Dermietzel R. Eur. J. Neurosci. 2005; 21:3277–3290. [PubMed: 16026466]
231. Huang Y, Grinspan JB, Abrams CK, Scherer SS. Glia. 2007; 55:46–56. [PubMed: 17009242]
232. Zappalà A, Li Volti G, Serapide MF, Pellitteri R, Falchi M, La Delia F, Cicirata V, Cicirata F. Neuroscience. 2007; 148:653–667. [PubMed: 17692470]
233. Garré JM, Retamal MA, Cassina P, Barbeito L, Bukauskas FF, Sáez JC, Bennett MV, Abudara V. Proc. Nat. Acad. Sci. (USA). 2010; 107:22659–22664. [PubMed: 21148774]
234. Becker DL, McGonnell I, Makarenkova HP, Patel K, Tickle C, Lorimer J, Green CR. Dev. Gene. 1999; 24:33–42.
235. Lecanda F, Warlow PM, Sheikh S, Furlan F, Steinberg TH, Civitelli R. J. Cell Biol. 2000; 151:931–943. [PubMed: 11076975]
236. Richardson R, Donnai D, Meire F, Dixon MJ. J. Med. Genet. 2004; 41:60–67. [PubMed: 14729836]
237. Kjaer KW, Hansen L, Eiberg H, Leicht P, Opitz JM, Tommerup N. Am. J. Med. Gene. 2004; 127A:152–157.
238. Flenniken AM, Osborne LR, Anderson N, Ciliberti N, Fleming C, Gittens JE, Gong XQ, Kelsey LB, Lounsbury C, Moreno L, Nieman BJ, Petrson K, Qu D, Roscoe W, Shao Q, Tong D, Veitch GI, Voronina I, Vukobradovic I, Wood GA, Zhu Y, Zirngibl RA, Aubin JE, Bai D, Bruneau BG, Grynpas M, Henderson JE, Kenkelman RM, McKerlie C, Sled JG, Stanford WL, Laird DW, Kidder GM, Adamson SL, Rossant J. Development. 2005; 132:4375–4386. [PubMed: 16155213]
239. Chung DJ, Castro CH, Watkins M, Stains JP, Chung MY, Szejnfeld VL, Willecke K, Theis M, Civitelli R. J. Cell Sci. 2006; 119:4187–4198. [PubMed: 16984976]
240. Watkins M, Grimston SK, Norris JY, Guillotin B, Shaw A, Beniash E, Civitelli R. Mol. Biol. Cell. 2011; 22:1240–1251. [PubMed: 21346198]
241. Plotkin LI, Lezcano V, Thostenson J, Weinstein RS, Manolagas SC, Bellido T. J. Bone Miner. Res. 2008; 23:1712–1721. [PubMed: 18597631]
242. Inose H, Ochi H, Kimura A, Fujita K, Xu R, Sato S, Iwasaki M, Sunamura S, Takeuchi Y, Fukumoto S, Saito K, Nakamura T, Siomi H, Ito H, Arai Y, Shinomiya K, Takeda S. Proc. Natl. Acad. Sci. USA. 2009; 106:20794–20799. [PubMed: 19933329]

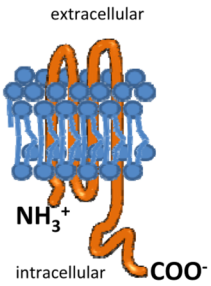
243. Rosselló RA, Wang Z, Kizana E, Krebsbach PH, Kohn DH. Proc. Natl. Acad. Sci. USA. 2009; 106:13219–13224. [PubMed: 19628695]
244. Zhang W, Green C, Stott NS. J. Cell Physiol. 2002; 193:233–243. [PubMed: 12385001]
245. Lecanda F, Towler DA, Ziambaras K, Cheng S-L, Koval M, Steinberg TH, Civitelli R. Mole. Biol. Cell. 1998; 9:2249–2258.
246. Jiang JX, Siller-Jackson AJ, Burra S. Front. Biosci. 2007; 12:1450–1462. [PubMed: 17127393]
247. Ziambaras K, Lecanda F, Steinberg TH, Civitelli R. J. Bone Miner. Res. 1998; 13:218–228. [PubMed: 9495514]
248. Romanello M, D'Andrea P. J. Bone Miner. Res. 2001:1465–1476. [PubMed: 11499869]
249. Plotkin LI, Bellido T. Cell Commun. Adhes. 2001; 2001:377–382. [PubMed: 12064622]
250. Plotkin LI, Manolagas SC, Bellido T. J. Biol. Chem. 2002:8648–8657. [PubMed: 11741942]
251. Genetos DC, Kephart CJ, Zhang Y, Yellowley CE, Donahue HJ. J. Cell. Physiol. 2007; 212:207–214. [PubMed: 17301958]
252. Siller-Jackson AJ, Burra S, Gu S, Xia X, Bonewald LF, Sprague E, Jiang JX. J. Biol. Chem. 2008; 283:26374–26382. [PubMed: 18676366]
253. Batra N, Burra S, Siller-Jackson AJ, Gu S, Xia X, Weber GF, DeSimone D, Bonewald LF, Lafer EM, Sprague E, Schwartz MA, Jiang JX. Proc. Natl. Acad. Sci. (USA). 2012 **[Epub ahead of print],**
254. Wang N, Butler JP, Ingber DE. Science. 1993; 260:1124–1127. [PubMed: 7684161]
255. Chen CS, Tan J, Tien J. Ann. Rev. Biomed. Eng. 2004; 6:275–302. [PubMed: 15255771]
256. Salter DM, Robb JE, Wright MO. J. Bone Miner. Res. 1997; 12:1133–1141. [PubMed: 9200014]
257. Burra S, Nicolella DP, Francis WL, Freitas CJ, Mueschke NJ, Poole K, Jiang JX. Proc. Natl. Acad. Sci. 2010; 107:13648–13653. [PubMed: 20643964]
258. Penuela S, Celetti SJ, Bhalla R, Shao Q, Laird DW. Cell Commun. Adhes. 2008; 15:133–142. [PubMed: 18649185]
259. Ishikawa M, Iwamoto T, Nakamura T, Doyle A, Fukumoto S, Yamada Y. J. Cell Biol. 2011; 193:1257–1274. [PubMed: 21690309]
260. Risley MS. Biol. Reprod. 2000; 62:748–754. [PubMed: 10684819]
261. Juneja SC, Barr KJ, Enders GC, Kidder GM. Biol. Reprod. 1999; 60:1263–1270. [PubMed: 10208994]
262. Francis RJB, Lo CW. Development. 2006; 133:3451–3460. [PubMed: 16887824]
263. Gilleron J, Carette D, Durand P, Pointis G, Segretain D. Int. J. Biochem. Cell Biol. 2009; 41:1381–1390. [PubMed: 19136074]
264. Winterhager E, Pielensticker N, Freyer J, Ghanem A, Schrickel JW, Kim JS, Behr R, Grümmer R, Maass K, Urschel S, Lewalter T, Tiemann K, Simoni M, Willecke K. BMC Dev. Biol. 2007; 7:26. [PubMed: 17408477]
265. Brehm R, Zeiler M, Rüttinger C, Herde K, Kibschull M, Winterhager E, Willecke K, Guillou F, Lécureuil C, Steger K, Konrad L, Biemann K, Failing K, Bergmann M. Am. J. Pathol. 2007; 171:19–31. [PubMed: 17591950]
266. Sridharan S, Simon L, Meiling DD, Cyr DG, Gutstein DE, Fishman GI, Guillou F, Cooke PS. Biol. Reprod. 2007; 76:804–812. [PubMed: 17229929]
267. Gilleron J, Nebout M, Scarabelli L, Senegas-Balas F, Palmero S, Segretain D, Pointis G. J. Cell Physiol. 2006; 209:153–161. [PubMed: 16823880]
268. Kidder GM, Mhawi AA. Reproduction. 2002; 123:613–620. [PubMed: 12006089]
269. Mitchell PA, Burghardt RC. Anat. Rec. 1986; 214:283–288. [PubMed: 3963423]
270. Eppig JJ. Biol. Reprod. 1991; 45:824–830. [PubMed: 1666849]
271. Eppig JJ, Obrien M, Wigglesworth K. Mol. Reprod. Dev. 1996; 44:260–273. [PubMed: 9115726]
272. Simon AM, Goodenough DA, Li E, Paul DL. Nature (Lond.). 1997; 385:525–529. [PubMed: 9020357]
273. Carabatsos MJ, Sellitto C, Goodenough DA, Albertini DF. Dev. Biol. 2000; 226:167–179. [PubMed: 11023678]

274. Ackert CL, Gittens JEI, O'Brien MJ, Eppig JJ, Kidder GM. Dev. Biol. 2001; 233:258–270. [PubMed: 11336494]
275. Dekel N. Ann. N. Y. Acad. Sci. 1988; 541:211–216. [PubMed: 2848437]
276. Chang AS, Dale AN, Moley KH. Endocrinology. 2005; 146:2445–2453. [PubMed: 15718275]
277. Johnson ML, Redmer DA, Reynolds LP, Grazul-Bilska AT. Endocrine. 1999; 10:43–51. [PubMed: 10403570]
278. Tong D, Li TY, Naus KE, Bai D, Kidder GM. J. Cell Sci. 2007; 120:4016–4024. [PubMed: 17971414]
279. Wörsdörfer P, Maxeiner S, Markopoulos C, Kirfel G, Wulf V, Auth T, Urschel S, von Maltzahn J, Willecke K. Stem Cells. 2008; 26:431–439. [PubMed: 18055446]
280. Todorova MG, Soria B, Quesada I. J. Cell Physiol. 2008; 214:354–362. [PubMed: 17654515]
281. Bhattacharya B, Cai J, Luo Y, Miura T, Mejido J, Brimble SN, Zeng X, Schulz TC, Rao MS, Puri RK. BMC Dev. Biol. 2005; 5:22. [PubMed: 16207381]
282. Liu Y, Shin S, Zeng X, Zhan M, Gonzalez R, Mueller FJ, Schwartz CM, Xue H, Li H, Baker SC, Chudin E, Barker SC, Chudin E, Barker DL, McDaniel TK, Oeser S, Loring JF, Mattson MP, Rao MS. BMC Dev. Biol. 2006; 6:20. [PubMed: 16672070]
283. Sperger JM, Chen X, Draper JS, Antosiewicz JE, Chon CH, Jones SB, Brooks JD, Andrews PW, Brown PO, Thomson JA. Proc. Natl. Acad. Sci. USA. 2003; 100:13350–13355. [PubMed: 14595015]
284. Huettner JE, Lu A, Qu Y, Wu Y, Kim M, McDonald JW. Stem Cells. 2006; 24:1654–1667. [PubMed: 16574755]
285. Wong RC, Pébay A, Nguyen LT, Koh KL, Pera MF. Stem Cells. 2004; 22:883–889. [PubMed: 15536180]
286. Boyer LA, Lee TI, Cole MF, Johnstone SE, Levine SS, Zucker JP, Guenther MG, Kumar RM, Murray HL, Jenner RG, Gifford DK, Melton DA, Jaenisch R, Young RA. Cell. 2005; 122:947–956. [PubMed: 16153702]
287. Wong RC, Dottori M, Koh KL, Nguyen LT, Pera MF, Pébay A. Biochem. Biophys. Res. Commun. 2006; 344:181–188. [PubMed: 16616002]
288. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Science. 1999; 284:143–147. [PubMed: 10102814]
289. Valiunas V, Doronin S, Valiuniene L, Potapova I, Zuckerman J, Walcott B, Robinson RB, Rosen MR, Brink PR, Cohen IS. J. Physiol. 2004; 555:617–626. [PubMed: 14766937]
290. Villars F, Guillotin B, Amédée T, Dutoya S, Bordenave L, Bareille R, Amédée J. Am. J. Phsiol. 2002; 282:C775–C785.
291. Jäderstad J, Jäderstad LM, Li J, Chintawar S, Salto C, Pandolfo M, Ourednik V, Teng YD, Sidman RL, Arenas E, Snyder EY, Herlenius E. Proc. Natl. Acad. Sci. USA. 2010; 107:5184–5189. [PubMed: 20147621]
292. Jäderstad J, Jäderstad LM, Herlenius E. Exp. Cell Res. 2011; 317:70–81. [PubMed: 20654614]
293. Jäderstad J, Brismar H, Herlenius F. Neuroreport. 2010; 21:1126–1132. [PubMed: 20938361]
294. Boucher S, Bennett SAL. J. Neuro. Res. 2003:393–404.
295. Goodall H, Maro B. Journal of Cell Biology. 1986; 102:568–575. [PubMed: 2868015]
296. Su JW, Tertoolen LG, de Laat SW, Hage WJ, Durston AJ. J. Cell Biol. 1990; 110:115–121. [PubMed: 2295681]
297. Taub R. Nat. Rev. Mol. Cell Biol. 2004; 5:836–847. [PubMed: 15459664]
298. Hoptak-Solga AD, Nielsen S, Jain I, Thummel R, Hyde DR, Iovine MK. Dev. Biol. 2008; 317:541–548. [PubMed: 18406403]
299. Vinken M, Decrock E, Leybaert L, Bultynck G, Himpens B, Vanhaecke T, Rogiers V. Biochim. Biophy. Acta. 2011 **[Epub ahead of print],**
300. Uyama N, Shimahara Y, Okuyama H, Kawada N, Kamo S, Ikeda K, Yamaoka Y. J. Hepatol. 2003; 39:749–755. [PubMed: 14568257]
301. Liu CL, Huang YS, Hosokawa M, Miyashita K, Hu ML. Chem. Biol. Interact. 2009; 182:165–172. [PubMed: 19737546]

302. Norris RP, Ratzan WJ, Freudzon M, Mehlmann LM, Krall J, Movsesian MA, Wang H, Ke H, Nikolaev VO, Jaffe LA. Development. 2009; 136:1869–1878. [PubMed: 19429786]
303. Vaccari S, Homer K, Mehlmann LM, Conti M. Dev. Biol. 2008; 316:124–134. [PubMed: 18280465]
304. Bopp T, Becker C, Klein M, Klein-Hessling S, Plametshofer A, Serfling E, Heib V, Becker M, Kubach J, Schmitt S, Stoll S, Schild H, Staege MS, Stassen M, Jonuleit H, Schmitt E. J. Exp. Med. 2007; 204:1303–1310. [PubMed: 17502663]
305. Oviedo-Orta E, Perreau M, Evans WH, Potolicchio I. J. Leukoc. Biol. 2010; 88:79–86. [PubMed: 20233983]
306. Wright CS, van Steensel MA, Hodgins MB, Martin PE. Wound Repair Regen. 2009; 17:240–249. [PubMed: 19320893]
307. Pollok S, Pfeiffer AC, Lobmann R, Wright CS, Moll I, Martin PE, Brandner JM. J. Cell Mol. Med. 2011; 15:861–873. [PubMed: 20345849]
308. Belliveau DJ, Bani-Yaghoub M, McGirr B, Naus CC, Rushlow WJ. J. Biol. Chem. 2006; 281:20920–20931. [PubMed: 16731531]
309. De Flora Z, Zocchi E, Guida L, Franco L, Bruzzone S. Ann. N. Y. Acad. Sci. 2004; 1028:176–191. [PubMed: 15650244]
310. Franco L, Zocchi E, Usai C, Guida L, Bruzzone S, Costa A, De Flora A. J. Biol. Chem. 2001; 276:21642–21648. [PubMed: 11274199]
311. Pearson RA, Dale N, Llaudet E, Mobbs P. Neuron. 2005; 46:731–744. [PubMed: 15924860]
312. Schenk U, Westendorf AM, Radaelli E, Casati A, Ferro M, Fumagalli M, Verderio C, Buer J, Scanziani E, Grassi F. Sci. Signal. 2008; 1:ra6. [PubMed: 18827222]
313. Iwamoto T, nakarmura T, Doyle A, Ishikawa M, de Vega S, Fukumoto S, Yamada Y. J. Biol. Chem. 2010; 285:18948–18958. [PubMed: 20404334]
314. Naus CCG, Bechberger JF, Caveney S, Wilson JX. Neurosci. Lett. 1991; 126:33–36. [PubMed: 1650934]
315. Jamieson S, Going JJ, D'Arcy R, George WD. J. Pathol. 1998; 184:37–43. [PubMed: 9582525]
316. Saunders MM, Seraj MJ, Li Z, Zhou Z, Winter CR, Welch DR, Donahue HJ. Cancer Res. 2001; 61:1765–1767. [PubMed: 11280719]
317. Zhu D, Caveney S, Kidder GM, Naus CC. PNAS. 1991; 88:1883–1887. [PubMed: 1848013]
318. Hirschi KK, Xu CE, Tsukamoto T, Sager R. Cell Growth Differ. 1996; 7:861–870. [PubMed: 8809403]
319. Yamasaki H, Omori Y, Zaidan-Dagli ML, Mironov N, Mesnil M, Krutovskikh V. Cancer Detec. Prev. 1999; 23:273–279. [PubMed: 10403898]
320. Moorby C, Patel M. Exp. Cell Res. 2001; 271:238–248. [PubMed: 11716536]
321. Qin H, Shao Q, Gurtis H, Galipeau J, Belliveau DJ, Wang T, Alaoui-Jamali MA, Laird DW. J. Biol. Chem. 2002; 277:29132–29138. [PubMed: 12042301]
322. Alexander DB, Ichikawa H, Bechberger JF, Valiunas V, Ohki M, Naus CC, Kunimoto T, Tsuda H, Miller WT, Goldberg GS. Cancer Res. 2004; 64:1347–1358. [PubMed: 14973064]
323. Zhang YW, Kaneda M, Morita I. J. Biol. Chem. 2003; 278:44852–44856. [PubMed: 12952975]
324. Zhang YW, Nakayama K, Morita I. Cancer Res. 2003; 63:1623–1630. [PubMed: 12670914]
325. Dang X, Jeyaraman M, Kardami E. Mol. Cell Biochem. 2006; 289:201–207. [PubMed: 16718370]
326. Kamibayashi Y, Oyamada Y, Mori M, Oyamada M. Carcinogenesis. 1995; 16:1287–1297. [PubMed: 7788845]
327. Miekus K, Czernik M, Sroka J, Czyz J, Madeja Z. Biol. Cell. 2005; 97:893–903. [PubMed: 15907197]
328. Tate AW, Lung T, Radhakrishnan A, Lim SD, Lin X, Edlund M. Prostate. 2006; 66:19–31. [PubMed: 16114058]
329. Kanczuga-Koda L, Sulkowski S, Lenczewski A, Koda M, Wincewicz A, Baltaziak M, Sulkowska M. J. Clin. Pathol. 2006; 59:429–433. [PubMed: 16567471]

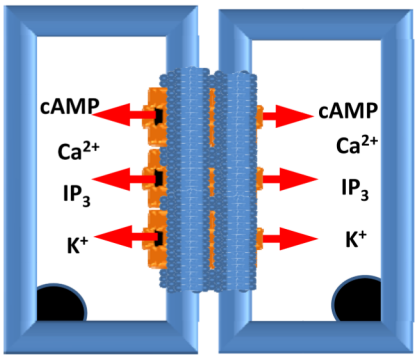
330. Zhang W, Nwagwu C, Le DM, Yong VW, Song H, Couldwell WT. J. Neurosurg. 2003; 99:1039–1046. [PubMed: 14705732]
331. Graeber SH, Hülser DF. Exp. Cell Res. 1998; 243:142–149. [PubMed: 9716458]
332. El-Sabban ME, Pauli BU. J. Cell Biol. 1991; 115:1375–1382. [PubMed: 1955478]
333. Ito A, Katoh F, Kataoka TR, Okada M, Tsubota N, Asada H, Yoshikawa K, maeda S, Kitamura Y, Yamasaki H, Nojima H. J. Clin. Invest. 2000; 105:1189–1197. [PubMed: 10791993]
334. de Vuyst E, Wang N, Decrock E, De Bock M, Vinken M, Van Moorhem M, Lai C, Culot M, Rogiers V, Cecchelli R, Naus CC, Evans WH, Leybaert L. Cell Calcium. 2009; 46:176–187. [PubMed: 19656565]
335. De Rivero Vaccari JC, Corriveau RA, BElousov AB. J. Neurophysiol. 2007; 98:2878–2886. [PubMed: 17855590]
336. Frank DK, Szymkowiak B, Josifovska-Chopra O, Nakashima T, Kinnally KW. Head Neck. 2005; 27:794–800. [PubMed: 15952193]
337. Huang R, Liu Y-G, Lin Y, Fan Y, Boynton A, Yang D, Huang R-P. Mol. Carcinog. 2001; 32:128–138. [PubMed: 11746825]
338. Huang RP, Hossain MZ, Huang R, Gano J, Fan Y, Boynton AL. Int. J. Cancer. 2001; 92:130–138. [PubMed: 11279616]
339. Sato H, Fukumoto K, Hada S, Hagiwara H, Fujimoto E, Negishi E, Ueno K, Yano T. Cancer Chemother. Pharmacol. 2007; 60:449–457. [PubMed: 17569045]
340. Seul KH, Kang KY, Lee KS, Kim SH, Beyer EC. Biochem. Biophy. Res. Comm. 2004; 319:1144–1151.
341. Tanaka M, Fraizer GC, De La Cerda J, Cristiano RJ, Liebert M, Grossman HB. Gene Ther. 2001; 8:139–148. [PubMed: 11313783]
342. Udawatte C, Ripps H. Apotosis. 2005; 10:1019–1029.
343. Wang M, Berthoud VM, Beyer EC. J. Cell Sci. 2007; 120:320–329. [PubMed: 17200141]
344. Hutnik CM, Pocrnich CE, Liu H, Laird DW, Shao Q. Invest. Ophthalmol. Vis. Sci. 2008; 49:800–806. [PubMed: 18235030]
345. Satomi Y, Nishino H, Shibata S. Anticancer Res. 2005; 25:4043–4047. [PubMed: 16309197]
346. Lee NP, leung KW, Wo JY, Tam PC, Yeung WS, Luk JM. Apoptosis. 2006; 11:1215–1229. [PubMed: 16699959]
347. Krysko DV, Mussche S, Leybaert L, D'Herde K. J. Histochem. Cytochem. 2004; 52:1199–1207. [PubMed: 15314087]
348. Cusato K, Ripps H, Zakevicius J, Spray DC. Cell Death Differ. 2006; 13:1707–1714. [PubMed: 16485029]
349. Krutovskikh VA, Piccoli C, Yamasaki H. Oncogene. 2002; 21:1989–1999. [PubMed: 11960371]
350. Boitano S, Dirksen ER, Sanderson MJ. Science. 1992; 258:292–295. [PubMed: 1411526]
351. Krysko DV, Leybasert L, Vandenabeele P, D'Herde K. Apoptosis. 2005; 10:459–469. [PubMed: 15909108]
352. Contreras JE, Sanchez HA, Veliz LP, Bukauskas FF, Bennett MV, Saez JC. Brain Res. Rev. 2004; 2004:290–303. [PubMed: 15572178]
353. Lee JR, DeRosa AM, White TW. J. Invest. Dermatol. 2009; 129:870–878. [PubMed: 18987669]
354. Li HY, Liu TF, Lazrak A, Peracchia C, Goldberg GS, Lampe PD, Johnson RG. J. Cell Biol. 1996; 134:1019–1030. [PubMed: 8769424]
355. Bao X, Reuss L, Altenberg GA. J. Biol. Chem. 2004; 279:20058–20066. [PubMed: 14973142]
356. Bertrand R, Solary E, O'Connor P, Kohn KW, Pommier Y. Exp. Cell Res. 1994; 211:314–321. [PubMed: 8143779]
357. Hur KC, Shim JE, Johnson RG. Cell Commun. Adhes. 2003; 10:271–277. [PubMed: 14681028]

Connexin



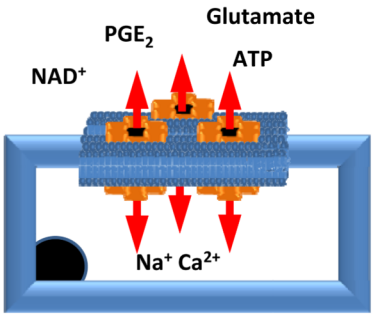
Role	Organ
Cell death	Brain, Inner ear, Kidney, Liver
Differentiation	Bone, Brain, Inner ear, Heart, Ovary, Lung, Liver
Proliferation/ survival	Brain, Bone, Heart, Lens, Ovary, Testis, Liver

Gap junction Channels



Role	Organ
Ionic conduction	Brain, Inner ear, Heart, Kidney, Lens, Lung, Liver
Metabolic coupling	Brain, Lens, Liver
2nd Messenger diffusion	Inner ear, Ovary, Lung, Liver

Hemichannels



Role	Organ
Injury protection	Heart
preconditioning	Brain, Heart
Extracellular cell signaling	Bone, Brain, Kidney, Ovary, Lung, Liver
Mechanical stimulation response	Bone, Ovary

Fig. 1. Gap junctions and hemichannels formed by the protein subunits, connexins play diverse roles in various organs and tissues

The top panel shows the role of connexins in regulating cell death, differentiation and overall survival of several organ systems. The middle panel describes the involvement of gap junction channels in ionic conduction, metabolic coupling and passage of second messengers in the different organ systems. The bottom panel summarizes the present knowledge of the role of hemichannels in regulating ionic conduction and overall response of cells of various organs to extracellular signaling, injury, ischemic preconditioning and mechanical stimulation.