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Review

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[2] [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 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

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[2] *Abbreviations used:* GJ, gap junctions; HC, hemichannels; GJIC, gap junction intercellular communication; CNS, central nervous system; ODDD, occulodentodigital dysplasia; ZO-1, zonula occludens-1; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; PTK, protein tyrosine kinases; OGD, oxygen–glucose deprivation; FasL, Fas ligands; BMD, bone mineral density; GCs, germ cells; mESCs, mouse embryonic stem cells; ECM, extracellular matrix; NSCs, neural stem cells; cADPr, cyclic ADP–ribose; APC, antigen presenting cells; PTH, parathyroid hormone; skp2, S phase kinase-associated protein 2; CaM, calmodulin; AA, arachidonic acid; KID, keratitis–ichthyosis–deafness; ST, staurosporine.

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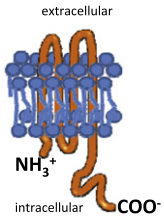
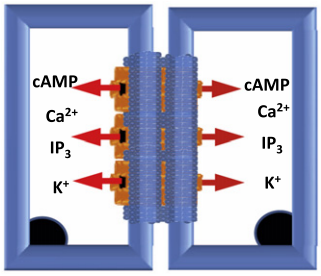
Connexin



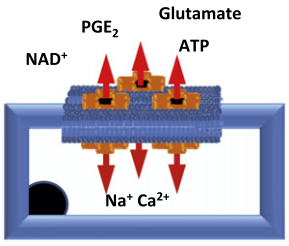
Role	Organ
Cell death	Brain, Inner ear, Kidney, Liver
Differentiation	Bone, Brain, Inner ear, Heart, Ovary, Lung, Liver
Proliferation/ survival	Brain, Bone, Heart, Lens, Ovary, Testis, Liver

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.

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].

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