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Review

Regulation of connexin expression by transcription factors and epigenetic mechanisms☆

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ABSTRACT

Gap junctions are specialized cell–cell junctions that directly link the cytoplasm of neighboring cells. They mediate the direct transfer of metabolites and ions from one cell to another. Discoveries of human genetic disorders due to mutations in gap junction protein (connexin [Cx]) genes and experimental data on connexin knockout mice provide direct evidence that gap junctional intercellular communication is essential for tissue functions and organ development, and that its dysfunction causes diseases. Connexin-related signaling also involves extracellular signaling (hemichannels) and non-channel intracellular signaling. Thus far, 21 human genes and 20 mouse genes for connexins have been identified. Each connexin shows tissue- or cell-type-specific expression, and most organs and many cell types express more than one connexin. Connexin expression can be regulated at many of the steps in the pathway from DNA to RNA to protein. In recent years, it has become clear that epigenetic processes are also essentially involved in connexin gene expression. In this review, we summarize recent knowledge on regulation of connexin expression by transcription factors and epigenetic mechanisms including histone modifications, DNA methylation, and microRNA. This article is part of a Special Issue entitled: The communicating junctions, roles and dysfunctions.

Contents

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1. Introduction

Gap junctions are specialized cell–cell junctions that directly link the cytoplasm of neighboring cells. They mediate the direct transfer of metabolites and ions from one cell to another. Therefore, it has long been hypothesized that gap junctional intercellular communication plays a crucial role in the maintenance of homeostasis, morphogenesis, cell differentiation, and growth control in multicellular organisms. Discoveries of human genetic disorders due to mutations in gap junction protein (connexin [Cx]) genes and experimental data on connexin knockout mice provide direct evidence that gap junctional intercellular communication is essential for tissue functions and organ development, and that its dysfunction causes diseases. Connexin-related signaling also involves extracellular signaling (hemichannels) and non-channel intracellular signaling.

Connexin proteins are named after their specific molecular weight in kDa (for instance, Cx43 has a mobility of 43 kDa). Twenty-one human genes and 20 mouse genes for connexins have been identified [1]. Their genes have been classified into 5 groups (alpha, beta, gamma, delta, and epsilon) based on sequence homology and thus the genes are named accordingly (for instance Cx43, which is the first connexin of the alpha-group, is coded by GJA1) (http://www.genenames.org/genefamilies/GJ). Each connexin shows tissue- or cell-type-specific expression, and most organs and many cell types express more than one connexin (Table 1). Some connexins, such as Cx32 and Cx43, are expressed in cells of many types, but others are expressed in very limited organs and cells. Even in the same tissue, the expression pattern of each connexin shows cell-type specificity and developmental changes, suggesting the presence of distinct but tight control mechanisms for regulation of connexin gene expression. For example, in the adult mouse heart tissue [2,3], Cx43, encoded by the *Gja1* gene, is expressed in all the cardiac components excluding the sinoatrial node (SAN) and atrioventricular node (AVN), the His bundle, and the proximal parts of the bundle branches (BBs). On the other hand, Cx40, encoded by *Gja5*, expression is restricted to the atrial myocytes, the AV node, and the His–Purkinje system. Similarly, Cx45, encoded by *Gjc1*, is restricted to the SAN and AVN, around the His bundle, and the most peripheral regions of the interventricular septum. Cx30.2, encoded by *Gjd3*, is expressed in the SAN and AVN, and to a lesser extent in the His bundle and its branches. Cx30.2 contributes to slow down impulse propagation in the AVN, and to limit the number of beats conducted from atria to ventricles. Cx30, encoded by *Gjb6*, is functionally expressed, in low abundance, in the SAN.

Cell coupling via gap junctions is dependent on the specific pattern of connexin gene expression [4]. This pattern of gene expression is altered during development and in several pathological conditions resulting in changes of cell coupling and probably connexin hemichannel function [5]. Like other genes, connexin expression can be regulated at many of the steps in the pathway from DNA to RNA to protein, i.e., transcriptional control, RNA processing control, RNA transport and localization control, translational control, mRNA degradation control, and protein activity control [6,7]. More recently the contributions of epigenetic and post-transcriptional mechanisms

Table 1
Human gap junction protein (connexin) genes.

Approved symbol	Approved name	Synonyms	Chromosome	Major expressed organ or cell types
GJA1	Gap junction protein, alpha 1, 43 kDa	Cx43	6q22-q23	Many cell types
GJA3	Gap junction protein, alpha 3, 46 kDa	Cx46	13q12.11	Lens
GJA4	gap junction protein, alpha 4, 37 kDa	Cx37	1p35.1	Endothelium, granulosa cells, lung, skin
GJA5	Gap junction protein, alpha 5, 40 kDa	Cx40	1q21.1	Cardiac atrium and conduction system, endothelium
GJA8	Gap junction protein, alpha 8, 50 kDa	Cx50	1q21.1	Lens
GJA9	Gap junction protein, alpha 9, 59 kDa	Cx59, Cx58	1p34	–
GJA10	Gap junction protein, alpha 10, 62 kDa	Cx62, mouse Cx57	6q15-q16	Retinal horizontal cells
GJB1	Gap junction protein, beta 1, 32 kDa	Cx32	Xq13.1	Hepatocytes, secretory acinar cells, Schwann cells
GJB2	Gap junction protein, beta 2, 26 kDa	Cx26	13q11-q12	Cochlea, placenta, hepatocytes, skin, pancreas, kidney, intestine
GJB3	Gap junction protein, beta 3, 31 kDa	Cx31	1p34	Cochlea, placenta, skin
GJB4	Gap junction protein, beta 4, 30.3 kDa	Cx30.3	1p35-p34	Skin, kidney
GJB5	Gap junction protein, beta 5, 31.1 kDa	Cx31.1	1p34.3	Skin
GJB6	Gap junction protein, beta 6, 30 kDa	Cx30	13q12	Astrocytes, cochlea
GJB7	Gap junction protein, beta 7, 25 kDa	Cx25	6q15	–
GJC1	Gap junction protein, gamma 1, 45 kDa	Cx45	17q21.31	SAN, AVN, smooth muscle cells, neurons
GJC2	Gap junction protein, gamma 2, 47 kDa	Cx47, Cx46.6,	1q41-q42	Oligodendrocytes, spinal cord, lymphatics
GJC3	Gap junction protein, gamma 3, 30.2 kDa	Cx30.2	7q22.1	Brain, spinal cord, Schwann cells
GJD2	Gap junction protein, delta 2, 36 kDa	Cx36	15q13.1	Neurons, pancreatic β-cells
GJD3	Gap junction protein, delta 3, 31.9 kDa	Cx31.9, Cx30.2	17q21.1	SAN, AVN
GJD4	Gap junction protein, delta 4, 40.1 kDa	Cx40.1	10p11.22	–
GJE1	Gap junction protein, epsilon 1, 23 kDa	Cx23	6q24.1	–