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Review

Gap junctional channels are parts of multiprotein complexes☆

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ABSTRACT

Gap junctional channels are a class of membrane channels composed of transmembrane channel-forming integral membrane proteins termed connexins, innexins or pannexins that mediate direct cell-to-cell or cell-to extracellular medium communication in almost all animal tissues. The activity of these channels is tightly regulated, particularly by intramolecular modifications as phosphorylations of proteins and via the formation of multiprotein complexes where pore-forming subunits bind to auxiliary channel subunits and associate with scaffolding proteins that play essential roles in channel localization and activity. Scaffolding proteins link signaling enzymes, substrates, and potential effectors (such as channels) into multiprotein signaling complexes that may be anchored to the cytoskeleton. Protein–protein interactions play essential roles in channel localization and activity and, besides their cell-to-cell channel-forming functions, gap junctional proteins now appear involved in different cellular functions (*e.g.* transcriptional and cytoskeletal regulations). The present review summarizes the recent progress regarding the proteins capable of interacting with junctional proteins and highlights the function of these protein–protein interactions in cell physiology and aberrant function in diseases. This article is part of a Special Issue entitled: The Communicating junctions, composition, structure and functions.

Contents

Abbreviations of cell lines: 42GPA9, mouse Sertoli cell line; βTC-3, mouse pancreatic β cell line derived from insulinomas; A431, human squamous carcinoma cells; A7r5, rat aortic smooth muscle cell line; BICR/M1R$_k$, a permanently growing cell line derived from a spontaneous rat mammary tumor; BWEM, rat cardiomyocyte-derived cells; C2C12, murine myoblasts; C6, rat glioma cell line; CHST8 cells, immortalized mouse hepatocytes; COS7, monkey African green kidney cells; E36, Chinese hamster ovary cells; FT210, a mutant cell line derived from FM3A a murine mammary carcinoma cell line; HEK 293, human embryonic kidney 293 cells; IAR20, rat epithelial cell line; J774, murine macrophage cell line; Jeg3, human choriocarcinoma cell line; LNCaP, human prostate cancer epithelial cells; MDCK, epithelial Madin–Darby Canine Kidney cells; Neuro2A, mouse neuroblastoma cells; N/N1003A, rabbit lens epithelial cells; NIH 3T3, mouse fibroblasts; NRK, rat kidney cells; N2a, murine neuroblastoma cells; P3/22, mouse skin papilloma cell line and its derivatives P3E1 (in which E-cadherin gene is transfected); PC-12 cell, a cell line substitute neuron originally cloned from rat pheochromocytoma cells; ROS 17/2.8, rat osteosarcoma cells; S180, mouse sarcoma cells; SW-13, human adrenal cortical tumor cells; T51B, rat liver epithelial cells; TtT/GF, murine pituitary folliculo-stellate-like cell line; U251, human glioblastoma cells; WB-F344, rat liver epithelial cells

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1. Introduction

Intercellular communication is of paramount importance in allowing individual cells to successfully act in a co-ordinated manner in multicellular organisms and tissues. Gap junctional intercellular communication (GJIC) relies on intercellular protein channels which span the lipid bilayers of contiguous cells, allowing them to directly exchange ions and small molecules. All junctional channels have a similar overall structure but, unlike many other membrane channels, different gene families encode the membrane proteins that form them in different animal phyla. The intercellular junctional channel is made by end-to-end docking of two hemichannels, each of which is an oligomer of transmembrane protein subunits, termed innexins (Inxs) in invertebrates, and connexins (Cxs) and pannexins (Panxs) in chordates (see [1]), forming an aqueous pore in the lipid bilayer. If pannexins were found able to form cell-to-cell channels in paired oocytes [2], an uncertainty remains on this capability in native tissues. Intercellular dye or electrical couplings are indeed generally absent in a variety of pannexin-expressing host cells (see [3]) but a Ca^{2+} wave propagation between osteoblasts was recently ascribed to Panx3 gap junctions [4].

Cxs, Inxs and Panxs have a common topology, with four alpha-helical transmembrane domains, two extracellular loops, a cytoplasmic loop, and N- and C-termini located on the cytoplasmic membrane face. Historically, the unpaired hemichannels scattered in nonjunctional membranes were considered as remaining permanently closed to avoid cell death, but several data reported in the past decade revealed that at least some of them mediated paracrine signaling by providing a flux pathway for ions such as Ca^{2+}, for ATP, glutamate and plausibly for other compounds, in response to physiological and pathological stimuli.

The properties of single membrane channels and intercellular channels are, as those of other membrane channels, determined by their 3-dimensional structure and related interactions with regulatory proteins. Structures that include channel-subunits and regulatory proteins depend on the microdomains that incorporate protein constituents. Multiprotein complexes associate pore-forming structures with scaffolding proteins that link signaling enzymes, substrates, and potential effectors (including channels) into a signaling complex anchored to the cytoskeleton. Besides an obvious role in targeting the channel to a particular location on the cell membrane, there are several advantages to having a membrane channel in a multiprotein complex. Indeed, the substrate selectivity of some enzymes, essential to determining specificity in several signal transduction pathways, is largely determined by their subcellular location (*e.g.* for protein kinases and phosphatases). There is also a large increase in the efficiency of the reaction kinetics when an enzyme is localized with its substrate and effector in a microenvironment with restricted diffusion. Moreover, the anchoring of enzyme complexes to some channels may be necessary for the extremely rapid transmission of signals required to regulate the activity of these channels. However, if the proteins in signaling cascades are considered spatiotemporarily organized in such a way to achieve efficiency and specificity, the physical association of components to form signaling complexes or their close proximity to facilitate random collisions still remains poorly understood and largely focused on Cx43, owing in large part to its ubiquitous distribution in mammalian tissues.

Many signaling pathways and regulatory systems in eukaryotic cells are controlled by proteins with multiple interaction domains that mediate specific protein–protein and protein–phospholipid interactions. Pairs of interacting partners at protein–protein (or protein–peptide) interfaces interact via modular protein domains that are well demarcated and independently folded domains, typically comprising 40 to 200 amino acids. These domains are non-catalytic and bind specifically to short continuous peptide sequences in their binding partner(s) via one or more exposed, ligand-binding surfaces ("ligand recognition pockets"). Ligands interact with their complementary domains through short and generally continuous sequence motifs. In some cases, certain amino acids of the ligands must be post-translationally modified (phosphorylated, acetylated, methylated,