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Biochimica et Biophysica Acta 1662 (2004) 1–2
BIOCHIMICA ET BIOPHYSICA ACTA
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Introduction

The connexins

Connexins form a diverse and ubiquitous family of integral membrane proteins present in both excitable and nonexcitable cells, forming in vertebrates intercellular channels which pack into discrete cell–cell contact areas termed gap junctions. Direct cell-to-cell communication via gap junction channels is certainly the simplest and the quickest of the various ways that cells 'talk' to one another. Composed of arrays of densely packed channels that connect the cytoplasmic compartments of neighbouring cells, gap junctions provide a direct route by which cells can exchange ions and molecules up to approximately 1kDa in size, including second messengers as Ca^{2+}, inositol phosphates, or cyclic nucleotides. These channels span two plasma membranes and result from the docking of two half channels, or connexons, which are hexameric torus of connexins around an aqueous pore. Twenty and twenty-one members of the connexin gene family are likely to be expressed in the mouse and human genome, respectively (19 of which can be grouped into sequence-orthologous pairs) and orthologues are increasingly characterised in other vertebrates. Most cell types express multiple connexin isoforms, making likely the construction of homo-oligomeric connexons, made of similar connexins, but different connexin polypeptide subunits can also assemble as hetero-oligomers. The ability to form homotypic and heterotypic channels that consist of two identical or two different connexons, respectively, adds even greater versatility to the functional modulation of gap junction channels, providing a structural basis for the charge and size selectivity of these intercellular channels.

The present issue of Biochimica et Biophysica Acta "Biomembranes", the first of two parts, presents an overview of some of the characteristics, properties and roles of connexin-made structures and some consequences of their dysfunction.

Morphological, genetic and functional studies have revealed that many connexins follow, for their synthesis, assembly and trafficking, the general secretory pathway for membrane proteins. Each connexin protein has four transmembrane domains, one intracellular and two extracellular loops, and cytoplasmically located carboxyl and amino termini. The six connexin molecules are most likely arranged so that their third transmembrane domains lines the channel lumen. The assembly of *connexin-made structures* appears to be based on specific signals located within the connexin polypeptides. Plaque formation by the clustering of gap junction channels in the plane of the membrane as well as channel degradation are still poorly understood processes. The number, size, and distribution of gap junctional channels is generally relatively stable under physiological conditions, but the flux of connexins into and out of gap junctions is frequently reported to be highly dynamic. The connexin turnover is unusually rapid, offering possibilities of adjustments of the degree of intercellular communication over a short period of time. The activity of many membrane channels also commonly requires the formation of multiprotein complexes, where pore-forming subunits bind to auxiliary proteins (e.g. scaffolding proteins), that play essential roles in channel localisation and activity.

Junctional channels have a similar overall structure but, according to their connexin composition, they may exhibit distinct physiological *properties*. The permeability and gating characteristics of gap junction channels are indeed dependent on the connexin isoform and on post-translational modifications present on them. In most cases, one connexin cannot fully substitute for another. Although many junctional channels are relatively nonselective in their permeability to ions and small molecules, some differences in permeability to cytoplasmic solutes (with potential biological consequences) have now been described. The level of cell-to-cell communication may be actively adjusted by multiple mechanisms including changes in connexin expression, regulation of connexin trafficking and turnover, and modulation of channel properties. Rather than being fixed passive conduits (as they were for a long time regarded), gap junction channels are, in fact, regulated by complex mechanisms that are only now being identified. The degree of intercellular communication is sensitive to a variety of stimuli, including changes in the level of intracellular Ca^{2+}, pH, in transjunctional applied voltage and in phosphorylation/dephosphorylation processes. Alterations in the phosphorylation status of proteins, resulting from the dynamic interplay of protein kinases and protein phosphatases, are indeed thought to be involved in a broad variety of connexin processes (such as the trafficking, assembly/disassembly, degradation, as well as the gating of junctional channels) but the underlying mechanisms still remain poorly understood.

Mediating the cell-to-cell diffusion of ions, metabolites, and small cell signalling molecules, junctional channels play

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doi:10.1016/j.bbamem.2004.02.001

pivotal *roles* in a wide range of physiological processes, for example in regulating events in development, cell differentiation, growth and proliferation, electrical activation of the heart and of smooth muscles or neuronal signalling, but also in hormone secretion, auditory function, wound healing, lens transparency or immune functions. Beside their actions as mediators of the transfer of small molecules between neighbouring cells, some connexins now appear to also have direct, gap junction-independent effects, for example on cell growth.

Consequently, defects in connexin proteins, and, therefore, in gap junctional communication, are associated with a large variety of *pathologies* in humans and experimental animals due to alterations in connexin expression and modulation of channel properties. On the other hand, the neuro- and cardioprotective effects of gap junction blocking agents demonstrate that closure of these channels may be beneficial in certain pathological situations. Connexins have also been shown to act as tumour suppressors, but their mechanism(s) of action remain unclear. Tumour growth inhibition was at first proposed to result from the diffusion of putative growth inhibitory factors via junctional channels, but connexins were also found able to directly alter gene expression.

The *hemichannels* present in the non-junctional regions of the plasma membrane are normally kept closed in the presence of normal extracellular Ca^{2+}, but it was recently reported that different cells can tolerate some hemichannel openings, which might exert physiological or deleterious effects, depending on the situation.

In conclusion, gap junctional channels, a unique structure found in most animal cell types, which span two cell membranes and the intercellular space, creating a conduit between the intracellular media of apposed cells and allowing the passive transfer on ions and small molecular weight molecules, are involved in a variety of cell functions. Gap junctional coupling was for a long time regarded as a ''static'' way of communication through stable intercellular tunnels before it appeared to be finely regulated. The importance of the rapid dynamics of channel turnover, of the plasticity of connexin expression and of the fine modulation of the channel permeability in response to various stimuli, offering possibilities for rapid remodelling of intercellular circuits, are now progressively gaining support.

Jean-Claude Hervé
UMR CNRS 6558, Faculté des Sciences,
Université de Poitiers, 40 Avenue du Recteur Pineau,
Poitiers Cedex 86022, France
E-mail address: Jean.Claude.Herve@univ-poitiers.fr
Tel./fax: +33-549-45-37-51