

Preface

The connexins

In animal tissues, most cells are connected via intercellular cytoplasmic channels clustered in plasma membrane spatial microdomains called gap junctions. Cell-to-cell channels, constructed of assemblies of channel proteins termed connexins or pannexins in vertebrates and innexins in invertebrates, allow the rapid exchange of ions and metabolites up to approximately 1 kD in size (including, for example, 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 Biophysica Acta* (BBA)—*Biomembranes*, the second of three parts, is designed to summarise some of the new information on some of the characteristics, properties and roles of connexin-made structures and on some consequences of their dysfunction.

Sosinsky and Nicholson [1] depict the molecular structure of gap junctional channels, dodecameric complexes in which a hexameric connexon in one plasma membrane docks end-to-end with a connexon in the membrane of a closely apposed cell to provide direct cell-to-cell communication.

Different connexins may oligomerise into single gap junctional channels, which display properties (e.g. gating activity, channel conductances, selectivity and regulatory behaviours) that sometimes are not predicted from the

functioning of the corresponding homogeneous channels. Cottrell and Burt [2] examine the functional consequences of heterogeneous gap junction channel formation and its influence in health and disease.

Connexons are embedded into lipid bilayers, a self-sealing assemblage of amphipathic phospholipids, sphingolipids, glycolipids, sterols and proteins in variable stoichiometries. The surrounding lipids influence the activity of membrane proteins via specific binding events and/or by their physicochemical properties. Cascio [3] overviews the available data on the effects of the bilayer and its constituent lipids on the activity of gap junctional channels.

Phosphorylation, a widespread post-translational modification of proteins, is a primary means of mediating signal transduction events that control numerous cellular processes via a highly regulated dynamic interplay of protein kinases and protein phosphatases. These processes appear implicated in the regulation of gap junctional communication at several stages of the connexin lifecycle, including intracellular connexin trafficking, connexon assembly and disassembly, connexin degradation as well as the gating of gap junction channels, but the underlying mechanisms remain poorly understood. Solan and Lampe [4] discuss how protein phosphorylation can regulate the early stages of the connexin life cycle through the assembly of functional gap junctional channels. Moreno [5] summarises available data concerning the importance of protein phosphorylation in the reversible process where a complete or relative closure or opening of a channel, termed gating, occurs. Laird [6] presents evidence that connexin phosphorylation regulates, stimulates or triggers gap junction disassembly, internalisation and degradation.

Gap junction communication is a prominent feature in the developing cerebral cortex as well as in the mature brain. The expression of connexins is important for both the formation of cell-to-cell channels allowing the transmission of functionally relevant molecules and also for the expression of genes encoding proteins of different functional categories. Iacobas et al. [7] examine the possibility for connexins to represent a central node

involved in the regulation of gene expression patterns in the brain.

Inflammatory cells respond to foreign substances and inflammatory stimulus by producing bioactive mediators such as prostanoids, cytokines and chemokines. These mediators have complex, pleiotropic effects and interact with many cell types to amplify the inflammatory response. Chanson et al. [8] present an overview of the involvement of gap junctional intercellular communication in tissue inflammation and repair.

Connexins form both intercellular channels, allowing cell-to-cell transfer of ions and essential metabolites, and hemichannels, able to act as independent functional units. But several lines of observations, summarised by Jiang and Gu [9], now support the notion that some connexin actions do not require the physical formation of gap junction channels.

Unapposed hemichannels were traditionally viewed as plasma membrane precursors of gap junctions, but recent findings suggested that they might open with a finite if low probability, providing a direct and nonselective pathway for the communication between the cytoplasm and the extracellular, an opening which is functional or deleterious depending on the situation. Saez et al. [10] summarise available data on the mechanisms of hemichannel gating.

As gap junctional communication represents an ubiquitous and integral part of multicellular organisms, one may imagine highly conserved components. Paradoxically, however, the connexin family appears to be confined to chordate lineages and no Cx homologues have been found in the fully sequenced genomes of *Drosophila* and *Caenorhabditis elegans*, which, instead, express invertebrate connexins, or innexins. Intriguingly, functional innexin homologues have also been found in vertebrate genomes. Phelan [11] overviews the current knowledge available concerning innexins.

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