Connexins and pannexins

Overview: Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport (see Evans and Martin, 2002; Bruzzone *et al*., 2003; Connors and Long, 2004). Gap junction channels allow the passive diffusion of molecules of up to 1000 Da that can include nutrients, metabolites and second messengers (such as IP_3) as well as cations and anions. Twenty-one connexin genes (Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59 and Cx62) and three pannexin genes (Px1, Px2 and Px3; which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction comprises two hemichannels or 'connexons' that are themselves formed from six connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells (see Herve *et al*., 2007). Connexins have a common topology, with four α-helical transmembrane domains, two extracellular loops, a cytoplasmic loop and N- and C-termini located on the cytoplasmic membrane face. In mice, the most abundant connexins in electrical synapses in the brain seem to be Cx36, Cx45 and Cx57 (Sohl *et al*., 2005). Mutations in connexin genes are associated with the occurrence of a number of pathologies, such as peripheral neuropathies, cardiovascular diseases and hereditary deafness. The pannexin genes Px1 and Px2 are widely expressed in the mammalian brain (Vogt *et al*., 2005). Like the connexins, at least some of the pannexins can form hemichannels (Bruzzone *et al*., 2003; Pelegrin and Surprenant, 2007).

	Connexins	Pannexins
Nomenclature	Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62	Px1, Px2, Px3
Ensembl ID	ENSG00000159248 (Cx36)*	ENSG00000110218 (Px1) ENSG00000073150 (Px2) ENSG00000154143 (Px3)
Inhibitors	Carbenoxolone Flufenamic acid Octanol Raising external calcium	Carbenoxolone Little block by flufenamic acid Unaffected by raising external calcium

Connexins are most commonly named according to their molecular weights, so, for example, Cx23 is the connexin protein of 23 kDa. This can cause confusion when comparing between species – for example the mouse connexin Cx57 is orthologous to the human connexin Cx62. No natural toxin or specific inhibitor of junctional channels has been identified; however, two compounds often used experimentally to block connexins are carbenoxolone and flufenamic acid (Salameh and Dhein, 2005). At least some pannexin hemichannels are more sensitive to carbenxolone than connexins but much less sensitive to flufenamic acid (Bruzzone *et al*., 2005). It has been suggested that 2-aminoethoxydiphenyl borate (2-APB) may be a more effective blocker of some connexin channel subtypes (Cx26, Cx30, Cx36, Cx40, Cx45 and Cx50) compared with others (Cx32, Cx43 and Cx46, Bai *et al*., 2006).

*Due to space constraints, the Ensembl ID for only Cx36 is given. Ensembl information for the other connexins can be found from links therein.

Further Reading

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