Chapter 2
Historical and Topological Perspective of Connexins

Preceding to the discovery of gap junction, it was observed that there might exist a pathway for direct cell–cell communication. Based on the work of Weidmann, it was observed that the space constant for the spread of current extends beyond the expected value for a single Purkinje fibre. Accordingly, it was suggested that this phenomenon might be due to the existence of a low-resistance intercellular channels. Further evidence supporting the existence of such intercellular channels was provided by the discovery of electric transmission at the giant crayfish motor synapses. These and other observations established that the cells of most invertebrate and vertebrate tissues are directly linked together by communicating channels mediated by low-resistance intercellular channels. In vertebrates, most of the cells form gap junctions except red blood cells, spermatozoa, and skeletal muscle. However, the progenitors of these cells are known to form gap junctions. Direct evidence for the existence of intercellular communicating channels was provided by the electron microscopic studies. It was observed that in excitable tissues, a current transfer between the adjacent cells only occurs when the plasma membrane of these cells was in close proximity and no such electric transmission was detected when the cells were not in close proximity with each other. Further studies confirmed the existence of such intercellular channels, and these were assigned several names, like nexus, macula communicans, and finally gap junction.

The gap junctions' topology has been significantly elucidated using electron microscopy and other biochemical strategies. Transmission electron micrography indicates that the gap junctions assemble in the regions where the plasma membranes of adjacent cells closely approach each other with a small gap of about 2–3.5 nm (Fig. 2.1). Freeze-fracture electron micrography of vertebrate junctions reveals that on the P-face, particles of 8.5 to 9.5 nm exist either singly or in plaque-like arrays with complementary pits on the E-face. Similarly, atomic force microscopy (AFM) indicates a dense packing of particles with a centre-to-centre distance of 9–10 nm. Based on these studies, it was demonstrated that these particles contain a pore-like structure with a diameter of 2 nm, a depth of 1 nm, and a width of 3.8 nm. According to X-ray diffraction studies and Fourier analysis, the gap junction forms a hexagonal

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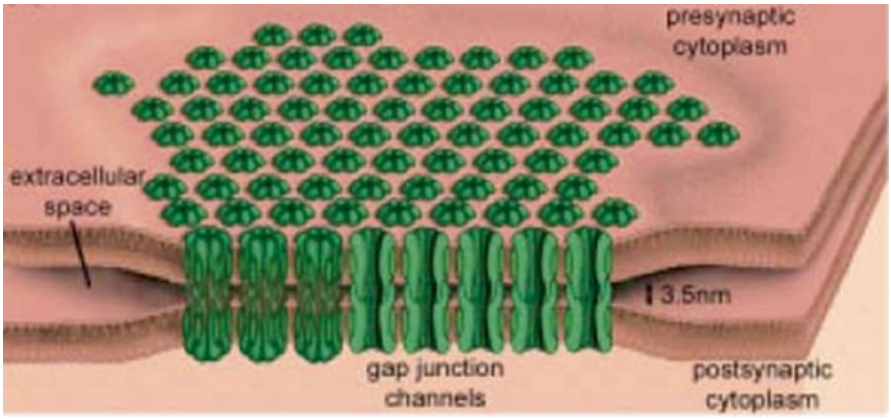

Fig. 2.1 Gap junction channel. Gap junction channels assemble in plaques containing few to several hundred single channels. Each cell contributes one hemichannel called connexon that consists of six connexin proteins. The gap junction channels span a small gap (3.5 nm) between the cell membranes and connect the cytoplasm of neighbouring cells

twisted cylinder with an apparent aqueous pore in the centre. The structure of the gap junction channel has been refined in recent years by using various genetic engineering approaches. Recombinant gap junction proteins and various truncated and mutated versions paved way for elucidating the finer structural details of these channels. Expression and purification of gap junction proteins led to their structural analysis using X-ray crystallographic techniques. In one such study, the X-ray crystallographic structure of a gap junction, at a resolution of 7 A^0, indicates that each hemichannel contains 24 α-helices corresponding to the four transmembrane domains of the six protein subunits.

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