UNIVERSITÀ DEGLI STUDI DI PADOVA

SHANGHAI SUMMER SCHOOL
VENICEASIAGO2016

DATE: 29th August 2016
TIME: 9:00 - 12:00
LOCATION: Osservatorio Astronomico di Asiago, via dell'Osservatorio, 8; Asiago, Vicenza

Biochemistry and Biophysics of communication between cells

Prof. Fabio Mammano
CNR Institute of Cell Biology and Neurobiology, Rome

ABSTRACT

Connexin-made channels are essential and widespread constituents of the cell-cell communication pathways that enable the direct exchange of nutrients and signaling molecules between adjacent cells [1] or between cell cytoplasm and the extracellular medium [2, 3]. Channel constituents are structurally homogeneous plasma membrane proteins encoded by twenty one connexin genes in the human genome [4].
Connexin proteins share the same topology, which comprises four transmembrane domains (TM1–TM4) connected by two extracellular loops (EC1 and EC2) and a cytoplasmic loop (CL), while the N– and C–termini (NT, CT) of the protein extend into the cytoplasm of the cell [5]. Connexins are post–translationally oligomerized to form hexameric assemblies, known as connexons or hemichannels which are then trafficked to the plasma membrane.
Typically, connexons from one cell seek to partner and dock with connexons from adjacent cells to form an intercellular (gap junction) channel [1]. These channels are characterized by an aqueous pore with a diameter typically > 1 nm [5, 6] and are permeable to all current–carrying anions and cations and low molecular weight molecules as well as some of the more important second messengers and paracrine factors involved in cell signaling [7, 8]. Unpaired connexin hemichannels in the cell plasma membrane lack ion selectivity and mediate autocrine/paracrine signaling by the release or uptake of small molecules which are critical for cell-cell communication and the regulation of the key inflammatory responses [3, 9].

Mutations leading to changes in properties, regulation or expression of connexin–made channels have been implicated in a variety of human diseases that can affect nearly every human organ [10]. In particular, mutations in GJB2 (MIM# 121011), the gene that encodes human connexin 26 (hCx26, where 26 indicated the molecular weight of the protein in kDa), are directly responsible for congenital sensorineural hearing loss; one of the most prevalent inherited diseases in the world [11]. Most current pharmacological agents for connexin and pannexin inhibition are notoriously nonspecific, making it difficult to consider them in therapeutic designs. Therefore there is an urgent need for more selective connexin inhibitors and activators with defined mechanisms of action.

REFERENCES and FURTHER READINGS

1. Goodenough DA, Paul DL. Gap junctions. *Cold Spring Harbor perspectives in biology*. 2009;1:a002576
2. Bennett MV, Contreras JE, Bukauskas FF, Saez JC. New roles for astrocytes: Gap junction hemichannels have something to communicate. *Trends Neurosci*. 2003;26:610-617
3. Saez JC, Leybaert L. Hunting for connexin hemichannels. *FEBS letters*. 2014;588:1205-1211
4. Sohl G, Willecke K. Gap junctions and the connexin protein family. *Cardiovascular research*. 2004;62:228-232
5. Maeda S, Nakagawa S, Suga M, Yamashita E, Oshima A, Fujiyoshi Y, Tsukihara T. Structure of the connexin 26 gap junction channel at 3.5 a resolution. *Nature*. 2009;458:597-602
6. Zonta F, Polles G, Zanotti G, Mammano F. Permeation pathway of homomeric connexin 26 and connexin 30 channels investigated by molecular dynamics. *Journal of biomolecular structure & dynamics*. 2012;29:985-998
7. Harris AL. Connexin channel permeability to cytoplasmic molecules. *Progress in biophysics and molecular biology*. 2007;94:120-143
8. Hernandez VH, Bortolozzi M, Pertegato V, Beltramello M, Giarin M, Zaccolo M, Pantano S, Mammano F. Unitary permeability of gap junction channels to second messengers measured by fret microscopy. *Nature methods*. 2007;4:353-358
9. Vinken M. Connexin hemichannels: Novel mediators of toxicity. *Archives of toxicology*. 2015;89:143-145
10. Kelly JJ, Simek J, Laird DW. Mechanisms linking connexin mutations to human diseases. *Cell and tissue research*. 2015;360:701-721
11. Zonta F, Girotto G, Buratto D, Crispino G, Morgan A, Abdulhadi K, Alkowari M, Badii R, Gasparini P, Mammano F. The p.Cys169tyr variant of connexin 26 is not a polymorphism. *Human molecular genetics*. 2015;24:2641-2648.