

Connexins and human diseases

Paolo Gasparini

Medical Genetics, Department of Reproductive Sciences and Development, IRCCS-Burlo-Garofolo, University of Trieste, Trieste, Italy

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Connexins are a large family of proteins involved in formation of gap junctions which allow the direct transfer of small molecules and ions between neighboring cells. Transmission at gap junction synapses is very fast allowing the production of almost instantaneously action potentials. Gap junctions are rare between mammalian neurons, but are common in non-neural cells, such glia, epithelial cells and smooth and cardiac muscle cells. There are three groups of connexins named alpha, beta, and non alpha-beta. Each connexin is identified by a number directly related to its molecular weight. Connexins form hexameric hemichannels (termed "connexons") in the endoplasmic reticulum, which are then translocated into the plasma membrane. The connexon then "docks" with a connexon of an adjacent cell to form a functional channel termed a "gap junction." Connexons can form either homotypic, heterotypic, or heteromeric channels. Connexins are expressed in many different tissues, including skin and inner ear. In the epidermis, gap junctions appear to play a role in the coordination of keratinocyte growth and differentiation, whereas there are several arguments supporting that gap junctions have an important role in the auditory transduction. The auditory organ has gap junctions between the outer hair cells and supporting cells (including melanocytes), providing a morphological basis for the

occurrence of intracellular responses to sound in supporting cells and for electric coupling of receptor cells. The endothelium of the scala media of the cochlea is involved in the production of a receptor response to the auditory stimulus and is separated from the endolymphatic space by tight junctions in the marginal cell layer, which is coupled by gap junctions. Immunohistochemical and ultrastructural analysis of some members of this protein family (connexin 26) in the rat cochlea showed that gap junctions in both epithelial and connective tissue cells are involved in recycling endolymphatic potassium ions. The identification of mutations in several connexin genes in patients with sensorineural hearing loss definitively confirm the involvement of gap junctions in the endocochlear potential of audition. Mutations in the gap-junction genes encoding the connexins have been also shown to cause epidermal disease, peripheral neuropathy, cataract and heart diseases. An up-to-date state of the art on connexins patterns of expression and related diseases will be presented and discussed.

Correspondence: Paolo Gasparini
Medical Genetics,
IRCCS - Burlo - Garofolo,
University of Trieste, Trieste, Italy
E-mail: gaspari@tigem.it