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Connexin and Pannexin large-pore channels as potential therapeutic targets in drug discovery

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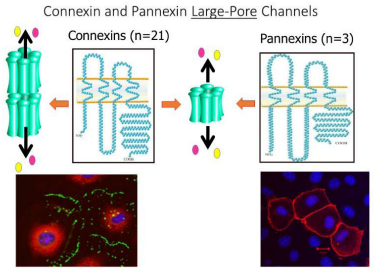

The connexin and pannexin families of large-pore forming channel proteins facilitate the passage of various ions, metabolites and signaling molecules between cellular cytoplasm, either through extrusion into the extracellular milieu or in the case of connexins, directly between cells. Connexins may functionally overlap with the activities of pannexin channels by participating in intercellular signaling by generating functional hemichannels at the cell surface, although this is not well documented *in vivo*. Connexin expression and regulation is tightly correlated with cancer onset and progression while mutations in half of the genes that encode the 21-member connexin gene family lead to over two dozen diseases ranging in severity from manageable developmental abnormalities to life-shortening organ failure. Our laboratory used tissue-relevant cells, primary cells, organotypic cultures, mouse models of human disease and induced pluripotent stem cells from connexin-linked disease patients to uncover ten distinct mechanisms by which connexin gene mutations cause disease. These mechanisms are subdivided into both gain- and loss of function mutations. Once mechanistic information is known as to how mutant connexins cause disease, long-term goals include developing strategies to compensate for cellular defects triggered by these mutants. Complementary to these connexin studies, pannexin expression levels and regulation has been linked to over a dozen diseases that affect most of the major organs in the human anatomy. Since these channels function at the cell surface and pannexin polypeptide domains are exposed to the extracellular surface, they represent potentially druggable targets. This presentation will discuss pannexins and connexins as therapeutic targets in disease treatment.

Recent Publications

1. E R Press, Q Shao, J J Kelly, K Chin, A Alaga and D W Laird (2017) Induction of cell death and gain-of-function properties of connexin-26 mutants predict severity of skin disorders and hearing loss. Journal of *Biological Chemistry*; 292: 9721-9732.
2. J L Esseltine, Q Shao, C Brooks, J Sampson, D Betts, C Seguin and D W Laird (2017) Connexin43 mutant patient-derived induced pluripotent stem cells exhibit altered differentiation potential. *Journal of Bone and Mineral Research;* 32: 1368-1385.

Biography

Dale W Laird is a Professor and Canada Research Chair in Gap Junctions and Disease. He has over 30 years of experience working with connexins and more recently pannexins and has published over 150 papers on their role in health and disease. He has received many awards for his research and is currently funded by the Canadian Institutes of Health Research.

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