Abstract

To maintain proper communication between pre- and postsynaptic sites, neurons are equipped with accessory molecules such as cell adhesion molecules (CAMs). Apart from the basal neurotransmission machinery, these CAMs also help maintain stringent control of synaptic transmission. Claudins are a family of CAMs that have not been well studied for their function at the synapse. The claudin super-family consists of four transmembrane domain proteins, which are important functional and structural components of tight junctions. They maintain paracellular permeability and barrier functions across epithelial and endothelial cells. Recent reports indicate their functional roles in the brain and in brain disorders. However, how they function in the brain and at the synapses is poorly understood. In the current study, we have discovered that a novel cell adhesion molecule HIC-1, a claudin homolog in C.elegans, is required to maintain normal post-synaptic acetylcholine receptor (AChR/ACR-16) levels through modulating the Wnt signalling pathway. Although, the Wnt signalling pathway that regulates AChR/ACR-16 localisation in the muscle has been well characterised, the mechanism of how Wnt secretion is regulated from C. elegans motor neurons is still largely unknown. We observed that the claudin homolog is involved in Wnt secretion at the Neuromuscular junction. Further, we found that the claudin homolog is expressed in cholinergic neurons and the mutant worms show increased levels of the acetylcholine receptor (AChR/ACR-16) at the NMJ. Our results indicate that the claudin functions in maintaining Wnt signalling as mutants in the Wnt regulator, wntless/mig-14, completely suppresses the claudin mutant phenotype. Further, our data also indicates that the claudin homolog affects the actin cytoskeleton and we hypothesise that through its role in modulating the actin cytoskeleton, HIC-1 could affect Wnt secretion. In the series of experiments to decipher the role of HIC-1 in the nervous system, we found that HIC-1 interacts with an actin binding protein Neurabin through its C-terminal PDZ interacting domain. Further, double mutant analysis revealed that NAB-1 and HIC-1 are involved in the same signalling pathway which regulates the actin cytoskeleton and Wnt secretion from the cholinergic neurons. In summary, we have unearthed an as yet uncharacterised C. elegans claudin, that functions as a neuromodulator by affecting post-synaptic AChR/ACR-16 levels at the NMJ through its function in pre-synaptic ACh neurons.