Extrinsic regulation of synaptic connectivity and neural circuit hyper-excitability by cell polarity proteins

Salvatore Cherra, PhD [1] • Yishi Jin, PhD [2]

[1]Neuroscience, UK hospital - Neuroscience • [2]Neurobiology, University of California, San Diego

Abstracts will be considered for both poster and platform presentations

Epilepsy/Brain metabolism

Robust regulation of neural circuit activity is essential to maintain proper brain function. Aberrant neuronal activity underlies multiple neurological disorders, including several types of epilepsies. To better understand how neural circuit activity is modulated in vivo, we have used the neuromuscular junction of Caenorhabditis elegans as a model. C. elegans is a translucent and genetically tractable animal with a rich repertoire of behaviors and a complete map of all connections in the nervous systems, thus making it an excellent system to study neural circuit function in vivo. Additionally, familial epilepsy-associated mutations in human and C. elegans acetylcholine receptors perturb neuronal activity patterns leading to hyper-activation of neural circuits. Using a disease-associated mutation in the acetylcholine receptor homolog, ACR-2, that causes hyper-excitability in C. elegans, we have previously identified new regulators of neuronal activity. Here, we have identified members of the cell polarity pathway as modulators of synaptic connectivity and neural circuit function. Cell polarity proteins normally establish intercellular junctions that guide the development of all tissue systems; however, their roles in the nervous system are not fully understood. MAGU-2, a homolog of the cell polarity protein Pals1/Mpp5, plays a role in limiting neuronal hyper-activity. Using a GFP tagged transgene, we observed expression of MAGU-2 throughout the animal; however, we did not detect MAGU-2 expression in neurons. Instead, we found MAGU-2 expressed in non-neuronal epidermal cells adjacent to neuromuscular junctions. Previous work has shown that the epidermis functions similar to mammalian glial cells in its ability to regulate neuronal function. MAGU-2 regulates the number of cholinergic synapses but not GABAergic synapses at the neuromuscular junction. We found that MAGU-2 specifically regulates the cell-cell junctions between neurons and epidermal cells that enable the removal of synapses by the epidermis. Mutations in MAGU-2 reduce cell adhesion proteins at epidermal-neuronal junctions and prevent the removal of cholinergic synapses at the neuromuscular junction. The increased connectivity of the cholinergic system in magu-2 mutants exacerbates the hyperactivity caused by the epilepsy-associated mutation in ACR-2. Overall, we have uncovered a new mechanism that enables non-neuronal cells to regulate neural activity in vivo. Understanding the roles of cell-cell junctions may provide additional insights into how non-neuronal cells limit neural hyper-excitability associated with neurological disorders.