Local control of synaptic protein synthesis in neurons by microRNAs

Supervisory team:
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Project description:
Neurons are a unique cell type because they are extremely polarised, with long processes extending millimetres from the nucleus in the cell body. This poses a cell biological challenge: how is protein expression at distal synapses regulated? One solution is that translation is locally controlled in dendrites to supply proteins according to the requirements of specific synapses. MicroRNAs (miRNAs) are small, endogenous RNAs that repress the translation of target mRNAs, and are fundamentally important for numerous cellular processes. Long-term synaptic plasticity underlies learning and memory by modifying neural circuitry, a major component of which is morphological changes of dendritic spines, which contain the postsynaptic machinery. Regulated miRNA activity plays a key role in this process by controlling the synthesis of proteins that determine spine morphology. MiRNA dysregulation is implicated in several neurological disorders that involve synaptic dysfunction, including Alzheimer's, Parkinson's, ALS and others. A key question is how "local" is this control of translation, i.e., does gene silencing spread to neighbouring unstimulated synapses, and if so, how is this regulated? This is important because theories of Hebbian learning assume that plasticity is synapse-specific, while emerging evidence suggests otherwise. We have recently defined mechanisms for rapidly increasing miRNA mediated gene silencing in response to synaptic stimulation to cause dendritic spine shrinkage. Our hypothesis is that miRNA activity is modulated close to the stimulated spine to locally regulate translation and influence the morphology of only a few spines. The main experimental approaches will be single-synapse stimulation of neurons followed by state-of-the-art cell imaging techniques to analyse sites of nascent protein synthesis and the dynamics of spine morphology in that region of dendrite. The project will investigate the mechanisms involved via mutagenesis of essential proteins such as Argonaute. In addition, molecular-level computer simulation models will be developed to test our hypotheses and dissect parts of the system that are not experimentally dissociable. This joint experimental-computational project will discover novel mechanisms of local regulation of protein synthesis at synapses during learning and memory processes. We are looking for an enthusiastic and innovative student with a degree in neuroscience, biological or medical science. The project will be supervised by Prof. Jonathan Hanley (neuronal cell biology) and Dr. Cian O'Donnell (computational biology). The cell imaging will be carried out in the excellent Wolfson Bioimaging Facility at the University of Bristol, with the expert assistance of their technical team. For further information, please contact Jonathan Hanley (jon.hanley@bristol.ac.uk).