Phosphoregulation of Argonaute function in synaptic plasticity and memory

Supervisory team:
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Project description:

MicroRNAs (miRNAs) are fundamentally important for fine-tuning protein synthesis by associating with Argonaute (Ago) proteins in the RNA-induced silencing complex (RISC) to repress the translation of target mRNAs. 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 modulating the translation of numerous synaptic proteins, and miRNA dysregulation is implicated in neurological disorders that involve synaptic dysfunction, such as Alzheimer's disease. Stimulation of postsynaptic NMDARs and consequent calcium-dependent intracellular signalling is the major upstream component of synaptic plasticity in the brain. Our recent in vitro work identified phosphorylation of Ago2 at Ser387 as an essential mechanism for regulating specific RISC protein-protein interactions and consequent miRNA-dependent gene silencing to control NMDAR-dependent dendritic spine plasticity (Rajgor et al., EMBO J., 2018).

In this project, we aim to investigate these mechanisms in vivo; we hypothesise that specific types of synaptic plasticity, and hence memory processes, require Ser387 phosphorylation-dependent changes in RISC protein-protein interactions and miRNA activity. To examine functional roles of Ago2 phosphorylation in synaptic plasticity and memory, this project will compare S387A (phospho-null) Ago2 knock-in mice with wild-type litter-mates in a battery of behavioural tests and brain slice synaptic electrophysiology assays. These will be chosen to assess a diverse range of learning and memory processes, which involve different types of synaptic plasticity. E.g. object recognition memory requires cortical long-term depression (LTD), or spatial memory involves hippocampal long-term potentiation (LTP). To define which miRNAs are involved, we will carry out Ago2 immunoprecipitations from lysates prepared from relevant brain regions, to analyse bound miRNAs by microarrays and RISC assembly by Western blotting. In addition, a proteomics screen will be carried out to analyse RISC protein-protein interactions in an unbiased manner. A role for RISC regulation by Ago2 phosphorylation in learning and memory is as yet unexplored, therefore this project will define novel concepts in miRNA-dependent mechanisms of brain function. It will also provide an excellent training in biochemistry, electrophysiology and behavioural neuroscience.

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 (biochemistry), Prof Clea Warburton (behavioural neuroscience) and Dr. Jon Brown (synaptic physiology). For further information, please contact Jonathan Hanley (jon.hanley@bristol.ac.uk).