Sequential elution interactome analysis of the Mind bomb 1 ubiquitin ligase reveals a novel role in dendritic spine outgrowth.

This is a study of an enzyme called mind bomb 1 (Mib1) E3 ubiquitin ligase – what a great name! E3 ubiquitin ligase is a family of enzymes consisting of about 500 proteins of which Mib1 is one. They are similar to kinases – such as CDKL5 - but instead of attaching phosphates to other proteins, they attach a small protein called ubiquitin, which is usually used as a signal for degradation – the breaking down of the protein. Mib1 appears to have many functions including a role in the embryonic development of the gastrointestinal tract, the limb buds and the immune system. In addition to this Mib1 is also abundantly expressed in the adult brain and plays an important role in neuronal morphogenesis.

In this study, the authors were looking to identify the set of molecular interactions that Mib1 is involved in– known as its interactome. During the first part of their study, the authors identified that amongst other things, Mib1 interacts with CDKL5. Studies were undertaken using particular types of research cell called HEK 293 cells. When expressed in these cells, CDKL5 is found to localise mainly in the nucleus. The authors showed that in the presence of Mib1, CDKL5 moves out of the nucleus and co-localises with Mib1 in the cytoplasm of the cell in aggregates known as cytoplasmic puncta. There is also a strong downregulation/degradation of CDKL5. In short, Mib1 ubiquitinates CDKL5 and alters its localization and abundance. This would therefore potentially alter the functional effects of CDKL5.

In further studies, the authors then looked at the interaction between CDKL5 and Mib1 on neuronal morphogenesis. Using cultured hippocampal neurons they found that CDKL5 caused an increase in spine density (an observation that corroborates previous studies) whilst Mib1 caused a decrease in spine density. They also observed that CDKL5 increased spine width and maturity. However, when CDKL5 and Mib1 were co-expressed the spine promoting effect of CDKL5 was removed. The effect of Mib1 on CDKL5 function appears to be due to its ligase activity.

Note – this is an interesting paper because we know that the function of the CDKL5 protein is thought to be regulated not just through synthesis/degradation but also through its subcellular localization – that is where in the cell it is. CDKL5 is thought to shuttle between the nucleus and the cytoplasm. The mechanisms for this are not understood yet and so this study may have identified one potential mechanism and therefore opened up avenues for further research.